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L2 ANSWER 1 OF 1 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
2004:328080 Document No.: PREV200400325706. Presence of staphylococcal exfoliative toxin A in sera of patients with atopic dermatitis. Yagi, S. [Reprint Author]; Wakaki, N.; Ikeda, N.; Takagi, Y.; Uchida, H.; Kato, Y.; Minamino, M.. Div Res and DevInst Cosmet Sci, Club Cosmet Co Ltd, 145-1 Ichibu Cho, Ikoma, Nara, 6300222, Japan. syagi@clubcosmetics.co.jp. Clinical and Experimental Allergy, (June 2004) Vol. 34, No. 6, pp. 984-993. print.
ISSN: 0954-7894 (ISSN print). Language: English.
AB Background It has been reported that the toxins that Staphylococcus aureus produces are associated with the exacerbation of atopic dermatitis (AD). It has been shown in many studies that staphylococcal enterotoxin (SE) A and SEB contribute to AD by humoral immunity through IgE production as a superantigen. On the other hand, little attention has been paid to the relationship between AD and exfoliative toxin x (**ETx**).
Objective We investigated the toxins that are frequently detected from the skin of patients and how these toxins affect AD. Methods S. aureus, isolated from the skin of 100 patients with mild to severe AD, were examined for the producibility of toxins by polymerase chain reaction. Serum samples were obtained from 21 patients with mild and moderate AD. The levels of SEB, ETA, total IgE, specific IgE, and specific IgG in sera were measured by ELISA. Results SEB was most frequently detected from S. aureus on the skin of these patients as previously reported. And **ETx**, to which little attention has been paid so far, was frequently detected next to SEB. Furthermore, ETA was detected from the sera of almost all the AD patients. SEB was not detected at all. Although the level of ETA in the AD group was significantly higher than that of controls, ETA-specific IgE was not detected from their sera. High levels of ETA tended to be detected from infantile patients. Although there were no significant differences in the levels of ETA-IgG between AD and the controls, its prevalence was more than twice as high as the controls in AD. Conclusion These results suggest that many AD patients were exposed to **ETx**. We conclude that **ETx** may contribute to exacerbation of AD, particularly in infants, by a mechanism that is not through specific IgE production, unlike SEB.

=> s Ctx
L3 13688 CTX

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L4 14 L3 AND ALLERGY

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L5 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
2005:99518 Document No. 142:204523 Agonist peptides of PAR-2, a human

receptor for zonulin and for Vibrio phage **CTX**.phi. ZOT, and uses to facilitate drug and antigen absorption, and in therpay and diagnosis. Fasano, Alessio; Vogel, Stefanie N. (University of Maryland, Baltimore, USA). PCT Int. Appl. WO 2005010022 A2 20050203, 55 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US22753 20040715. PRIORITY: US 2003-2003/PV487889 20030715.

AB The invention provides an agonist polypeptide of a human receptor of zonulin and Vibrio cholerae phage **CTX**.phi. ZOT (zonula occludens toxin) protein. The agonist can be used to facilitate drug and antigen absorption. Suitable routes of administration include oral, nasal, transdermal, and i.v. Pharmaceutical formulations may comprise a therapeutic agent or an immunogenic agent in combination with the agonist polypeptide. It was shown, that proteinase-activated receptor PAR-2 variant or homolog is the target receptor for both Zot and zonulin, and suggested that this receptor is involved in the regulation of intercellular tight junction. It was also shown, that Zot binds directly to the PAR-2 ECL2 and activates the receptor signaling, while zonulin may activate the target receptor by cleaving it at its N-terminus.

L5 ANSWER 2 OF 13 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

2003:357927 Document No.: PREV200300357927. Antibody to Ceftriaxone in HIV Pediatric Patients and Potential Implications for RBC Hemolysis. Bateman, Scot T. [Reprint Author]; Hu, Edward [Reprint Author]; Lane, Cathy [Reprint Author]; Quillen, Karen [Reprint Author]; Pelton, Stephen I. [Reprint Author]. Pediatrics, Boston University School of Medicine, Boston, MA, USA. Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 3656. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB Introduction: Ceftriaxone (**CTX**), a third generation cephalosporin, is commonly used for the treatment of suspected bacteremia in high risk patients because of its broad spectrum antibacterial activity and prolonged half-live. Significant complications of severe immune hemolytic anemia (IHA) secondary to parenteral **CTX** have recently been reported. Of the cases reported, 6/9 were in children and 5/6 were fatal. All of the patients were immunocompromised or had underlying chronic hematologic disorders - HIV infection, sickle cell disease, hypereosinophilic syndrome, or leukemia and had a history of receiving multiple courses of **CTX**. **CTX** appears unique in that all reported cases of ceftriaxone associated hemolysis have reacted only by the immune complex mechanism. This mechanism appears to produce the most fulminant clinical picture. The prevalence of **CTX**-induced drug-dependent RBC antibodies in an at-risk population has not previously been studied. Methods: All patients (age 1 yr to 21 yr) followed in the Pediatric HIV clinic were eligible to participate. IRB approval was obtained. Serum from clinical specimens after all tests for the patient's care were completed was used. The patient's serum was incubated in the presence of **CTX**, with and without the addition of fresh normal serum as a source of complement, with untreated and enyzme-treated donor RBCs. If enough serum was available, the testing was repeated with cefuroxime, another third generation cephalophorin, which has no IHA case reports . Positive agglutination or hemolysis in any of the patient's tests to which the drug was added, and a negative or significantly weaker result in the corresponding negative control tests suggested the presence of an antibody to the drug being studied. Additionally, we correlated our results with **CTX** exposure history on review of pt medical

record. Positive controls (sera known to contain **CTX**-induced RBC antibodies) and other technical assistance was obtained from the Immunohematology Research Laboratory at the American Red Cross Blood Services, Southern California Region. Results: 29 pediatric HIV pt were screened. Mean age was 10.8 yr (range of 3 to 19yr), mean number of treatment courses (q day dosing x 1-2 days up to 3wk/course) of **CTX** was 4 (+-3.8, range 0-20). Overall incidence of a positive (+) **CTX** dependent RBC antibody test was 14% (4/29). Another 24% (7/29) had non-interpretable (NI) results secondary to the presence of allo-or auto-antibodies. All three groups of pt were similar in respect to age (11.2 (+) vs. 11.4 (-) vs. 10.4 (NI)) as well as known drug **allergies**, baseline medications and known complications. Positive antibody patients had less exposure to **CTX** than (-) patients 2.3 vs. 5.1 courses, and similar to NI patients 2.1 courses. Thirteen patients were tested with cefuroxime (including 3/4 who tested + to **CTX**). 1/13 was positive (and also positive to **CTX**), 2/13 were NI (and also NI to **CTX**), and 10/13 negative (including 2/3 who were + to **CTX**). Conclusions: A significant number of pediatric HIV patients with repeated exposure to **CTX** appear to have the potential for IHA but the mechanism for its development remains unclear. A more thorough prospective investigation into the development and risk potential is warranted prior to making recommendations about drug therapy.

L5 ANSWER 3 OF 13 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
1996:145016 Document No.: PREV199698717151. Interferon gamma (IFN-gamma) inhibits neutrophil chemotaxis (**CTX**) without affecting generation of superoxide anion (SO). Kowalski, M. L.; Szkudlinska, B.; Pawliczak, R.; Iwaszkiewicz, J.. Lodz, Poland. Journal of Allergy and Clinical Immunology, (1996) Vol. 97, No. 1 PART 3, pp. 282.
Meeting Info.: Fifty-second Annual Meeting of the American Academy of Allergy Asthma and Immunology. New Orleans, Louisiana, USA. March 15-20, 1996.
CODEN: JACIBY. ISSN: 0091-6749. Language: English.

L5 ANSWER 4 OF 13 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
1996:356096 Document No.: PREV199699078452. Inhibition of neutrophil chemotaxis (**CTX**) by recombinant interferon gamma (rINF-gamma). Kowalski, M. L.; Szkudlinska, B.; Pawliczak, R.; Iwaszkiewicz, J.; Woszczek, G.. Lodz, Poland. Allergy (Copenhagen), (1996) Vol. 51, No. SUPPL. 31, pp. 33.
Meeting Info.: Annual Meeting of the European Academy of Allergology and Clinical Immunology. Budapest, Hungary. June 2-5, 1996.
CODEN: LLRGDY. ISSN: 0105-4538. Language: English.

L5 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
1996:266150 Document No. 124:332301 Immunomodulating effects of the extract from clam Meretrix meretrix on delayed hypersensitivity in mice. He, Yajun; Wu, Qian; Zhu, Reifei (Guangdong Province Institute Materia Medica, Canton, 510180, Peop. Rep. China). Zhongguo Haiyang Yaowu, 14(3), 020-1 (Chinese) 1995. CODEN: ZHYAE8. ISSN: 1002-3461. Publisher: Shandong Haiyang Yaowu Kexue Yanjiuso.
AB The immunomodulating effects of the extract from Meretrix meretrix on the delayed hypersensitivity (DH) in mice were studied. The results showed that the extract from Meretrix meretrix and its polysaccharides promoted the DH-decreasing effect of cyclophosphamide (**CTX**), and inhibited the DH-increasing effect of **CTX**.

L5 ANSWER 6 OF 13 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
DUPLICATE 1
1994:246123 Document No.: PREV199497259123. Cholera toxin (**CTX**) promotes IgE antibody and **allergy** during oral immunization. Snider, D. P.; Marshall, J. S.; Perdue, M. H.; Liang, H.. Dep. Pathology, MVIP, McMaster Univ., Hamilton, ON L8N 3Z5, Canada. FASEB Journal, (1994) Vol. 8, No. 4-5, pp. A282.

Meeting Info.: Experimental Biology 94, Parts I and II. Anaheim, California, USA. April 24-28, 1994.
CODEN: FAJOEC. ISSN: 0892-6638. Language: English.

L5 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
1991:239997 Document No. 114:239997 Antigenicity study of cefpirome sulfate. Inoue, Sachiko; Morioka, Hiroshi; Satoh, Ryoichi; Yoshida, Yasushi; Omosu, Mikio; Kobayashi, Takayoshi (Pharma Res. Lab., Hoechst Japan Ltd., Kawagoe, 350, Japan). Journal of Toxicological Sciences, 15(Suppl. 3), 129-45 (Japanese) 1990. CODEN: JTSCDR. ISSN: 0388-1350.
AB Immunol. properties of cefpirome sulfate (CPR) were examined The immunogenicity and challenging ability of CPR were examined in guinea pigs by active systemic anaphylaxis (ASA) and homologous 4-h passive cutaneous anaphylaxis (PCA) tests. The animals given CPR alone i.p. for sensitization and their sera were neg. for ASA or PCA reactions, like the results with reference substances, ceftazidime (CAZ) and cephalothin sodium (CET). When each antibiotic plus Freund's complete adjuvant (FCA) was used for sensitization, ASA reactions were observed with CPR, cephaloridine (CER), CET, and cefazolin sodium (CEZ), and PCA reactions, with CPR and CET. CPR had the ability to challenge the ASA and PCA reactions. CER and CET also showed the ability to challenge ASA or PCA reactions, though at low incidences. The cross-reactivity of CPR with com. available antibiotics was examined by heterologous PCA test and by passing hemagglutination test and its inhibition test. The antiserum used was from rabbits immunized with each antibiotic-ovalbumin conjugate plus FCA, and the antigen was each antibiotic-bovine serum albumin conjugate. CPR cross-reacted markedly with cefotaxime sodium (**CTX**) having the same side chain at position 7 and showed weak, unidirectional reactions with CAZ and CET. In the in vitro direct Coombs test, the pos. reactions noted with CPR were stronger than those with latamoxef sodium, equal to those with CEZ and slighter than those with **CTX**, CET and benzylpenicillin potassium. In conclusion, in the safety evaluation of CPR, its antigenic potential may not be a problem, like the cases of other antibiotics.

L5 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
1984:628385 Document No. 101:228385 Characterization of the delayed hypersensitivity response to a protein antigen in the mouse - I. Kinetics of reactivity and sensitivity to classical immunosuppressants. Holsapple, Michael P.; Page, Dennis G.; Bick, Peter H.; Shopp, George M. (Med. Coll. Virginia, Virginia Commonw. Univ., Richmond, VA, 23298, USA). International Journal of Immunopharmacology, 6(5), 399-405 (English) 1984. CODEN: IJIMDS. ISSN: 0192-0561.
AB Several parameters of the delayed hypersensitivity response (DHR) to a protein antigen, keyhole limpet hemocyanin (KLH), were investigated. Female B6C3F1 mice were sensitized with KLH suspended in either complete Freund's Adjuvant (CFA) or sterile saline. When the mice were sensitized twice, the magnitudes of these responses were equivalent as measured by a radioisotope procedure reflecting the influx of monocytes. With only a single sensitization, there was a 37% decrease in the response of CFA-treated mice and a dramatic (82%) decrease in the response of saline-treated mice. Utilizing 2 sensitizing injections in male CD-1 mice, the kinetics of the responses were determined to be equivalent regardless of whether KLH was suspended in CFA or saline in that both responses were persistent for up to 5 wks between the second sensitization and challenge. Ear thickness in CFA-treated mice was twice that of the saline-treated mice at 1, 3 and 5 wks. This increased swelling was not due to an increase in the vascular permeability as measured by the extravasation of a radiolabeled protein. There was a marked increase in the total area of fibrin in both sensitized groups when compared to unsensitized mice, but no difference between the groups. The sensitivity of these responses to immunosuppressants was determined in male CD-1 mice exposed subchronically (14 day) to dexamethasone (DEX) and cytoxan (**CTX**). There was a marked increase in the suppression by DEX in mice sensitized to KLH in

saline as compared to mice sensitized to KLH in CFA. In contrast, the sensitivity to suppression by cyclophosphamide was not affected by the presence of CFA.

L5 ANSWER 9 OF 13 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
1980:141815 Document No.: PREV198069016811; BA69:16811. DELAYED HYPER SENSITIVITY IN SURGICAL PATIENTS A MECHANISM FOR ANERGY. CHRISTOU N V [Reprint author]; MEAKINS J L. DEP SURG, R VICTORIA HOSP, ROOM S624, 687 PINE AVE W, MONTREAL, QUE 13A 1A1, CAN. Surgery (St Louis), (1979) Vol. 86, No. 1, pp. 78-85.
CODEN: SURGAZ. ISSN: 0039-6060. Language: ENGLISH.
AB Lymphocyte chemotaxis (**CTX**) was studied in 74 patients and 13 controls to assess whether or not failed delayed hypersensitivity (DH) skin test response might be due to a failure of recruitment of lymphocytes to the area of antigen deposition. Lymphocytes were obtained by Ficoll-Hypaque separation of leukocyte-rich plasma and used at a concentration of 3 + 106 cells/ml in minimal essential medium plus 10% fetal calf serum (MEM-FCS). **CTX** was assessed using 3 μm nitrocellulose filters, casein (5 mg/ml) in MEM-FCS as attractant, incubation at 37° C for 5 h and the leading front technique. In this system control lymphocytes migrated a distance of 106.4 ± 1.6 μm (n = 13, mean ± SE), whereas lymphocytes from anergic patients migrated 87.5 ± 1.3 μm (n = 35, P < 0.0005). Simultaneous determinations of lymphocyte **CTX** and PMN [polymorphonuclear leukocyte] **CTX** demonstrated that the 2 are highly correlated (X = 22.4 ± 0.67 Y, r2 = 0.7904, P < 0.0005). Anergic sera which decreased control PMN **CTX** from 128.1 ± 2.4 to 94.7 ± 1.5 μm also decreased control lymphocyte **CTX** from 112.1 ± 3.1 to 81.5 ± 2.4 μm (n = 13, P < 0.001). Stimulation index following blastogenic transformation of lymphocytes with phytohemagglutinin was similar for anergic patients (11.5) compared to controls (13) (P .apprx. 0.5). The failure of DH responses seen in surgical patients probably does not reflect classical cell-mediated immunity. This newly demonstrated defect in lymphocyte **CTX** in anergic patients, together with reduced neutrophil **CTX** (mediated by circulating serum inhibitors), apparently contributes to the observed failed DH response.

L5 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
1978:458241 Document No. 89:58241 The role of B lymphocytes in cell-mediated immunity. II. Delayed hypersensitivity induced by dinitrophenyl-Ficoll in dinitrophenyl-keyhole limpet hemocyanin-immunized guinea pigs. Rosenstreich, David L.; Wahl, Sharon M.; McMaster, Philip R. B. (Natl. Inst. Dent. Res., NIH, Bethesda, MD, USA). Cellular Immunology, 38(1), 116-23 (English) 1978. CODEN: CLIMB8. ISSN: 0008-8749.
AB Dinitrophenyl (DNP)-Ficoll will elicit typical delayed hypersensitivity skin reactions in guinea pigs immunized with DNP-keyhole limpet hemocyanin (KLH). Lymph node cells (LNC) from these animals produced the lymphokine, monocyte chemotactic factor (MNL **CTX**) when stimulated by DNP-Ficoll in vitro. This response was antigen and hapten specific since LNC from nonimmune guinea pigs or those immunized with nonDNP containing antigens were not stimulated by DNP-Ficoll. Lymph node cells were fractionated into T- and B-cell-enriched populations to determine the nature of the DNP-Ficoll-responsive cell. Only the B-lymphocyte-enriched population produced MNL **CTX** in response to DNP-Ficoll. The purity of the B-cell population was demonstrated by its failure to respond to PHA and by the fact that B cells derived from DNP-ovalbumin (OVA) immune guinea pigs responded to both lipopolysaccharide and to DNP-Ficoll, although they could no longer respond without T-cell help to the T-dependent antigen, DNP-OVA. These findings suggest that the hapten-specific response to guinea pigs to DNP-Ficoll may be a form of B-cell-mediated delayed hypersensitivity.

L5 ANSWER 11 OF 13 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
1978:165899 Document No.: PREV197865052899; BA65:52899. DELAYED HYPER

SENSITIVITY INDICATOR OF ACQUIRED FAILURE OF HOST DEFENSES IN SEPSIS AND TRAUMA. MEAKINS J L [Reprint author]; PIETSCH J B; BUBENIK O; KELLY R; RODE H; GORDON J; MACLEAN L D. ROOM S1030, 687 PINE AVE W, MONTREAL, QUE H3A 1A1, CAN. Annals of Surgery, (1977) Vol. 186, No. 3, pp. 241-250. CODEN: ANSUA5. ISSN: 0003-4932. Language: ENGLISH.

AB Primary failure of host defense mechanisms has been associated with increased infection and mortality. Anergy, the failure of delayed hypersensitivity response, identifies surgical patients at increased risk for sepsis and related mortality. The anergic and relatively anergic patients whose skin tests failed to improve had a mortality rate of 74.4%, whereas those who improved their responses had a mortality rate of 5.1% ($P < 0.001$). This study documents abnormalities of neutrophil chemotaxis, T [thymus-derived] lymphocyte rosetting in anergic patients and the effect of autologous serum. These abnormalities may account for the increased infection and mortality rates in anergic patients. Skin testing with 5 standard antigens identified 110 anergic (A) or relatively anergic (RA) patients in whom neutrophil chemotaxis (**CTX**) and bactericidal function (NBF), T lymphocyte rosettes, mixed lymphocyte culture (MLC), cell-mediated lympholysis (CML) and blastogenic factor (BF) were studied. The MLC, CML and BF were normal in the patients studied and were not clinically helpful. Neutrophil **CTX** in 19 controls was 117.5 $\pm$ 1.6 u [units], whereas in 40 A patients, neutrophils migrated 81.7 $\pm$ 2.3 u, and in 15 RA patients 97.2 $\pm$ 3.8 u ($P < 0.01$). In 14 patients whose skin tests converted to normal, neutrophil migration improved from 78.2 $\pm$ 5.4 u to 107.2 $\pm$ 4.0 u ($P < 0.01$). Incubation of A or control neutrophils in A serum reduced migration in A patients from 93 $\pm$ 3.7 u to 86.2 $\pm$ 3.5 u ($P < 0.01$) and in normals from 121.2 $\pm$ 1.6 u to 103.6 $\pm$ 2.6 u ($P < 0.001$). The percent rosette forming cells in 66 A patients was 42.5 $\pm$ 3.1 compared to 53.6 $\pm$ 2.8 in normal responders ($P < 0.02$). Incubation of normal lymphocytes in anergic serum further reduced rosetting by 30%. Restoration of delayed hypersensitivity responses and concurrent improvement in cellular and serum components of host defense were correlated with maintenance of adequate nutrition and aggressive surgical drainage.

L5 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN

1975:71504 Document No. 82:71504 Characterization of chemotactic activity produced in vivo by a cell mediated immune reaction in the guinea pig. Postlethwaite, Arnold E.; Snyderman, Ralph (Lab. Connect. Tissue Res., VA Hosp., Memphis, TN, USA). Journal of Immunology, 114(1), 275-9 (English) 1975. CODEN: JOIMA3. ISSN: 0022-1767.

AB The mechanisms of leukocyte accumulation in vivo were examined in guinea pigs exhibiting delayed hypersensitivity to horseradish peroxidase (HRPO). Within 24 hr of the i.p. injection of HRPO to such animals there was a significant increase in the number of peritoneal macrophages and in the chemotactic activity (**CTX**) for macrophages in the sampled peritoneal fluid. At 48 and 72 hr the **CTX** returned to the prechallenge level and i.p. macrophages appeared to be actively phagocytic. Mol. sieve chromatograms of concentrated peritoneal fluid obtained 24 hr after i.p. challenge with HRPO and of supernatants derived from immune spleen cells cultured in the presence of HRPO in vitro revealed that the major portion of **CTX** for homologous macrophages eluted in the region of the 12,500 dalton protein marker. The partially purified **CTX** obtained from peritoneal fluid and supernatants of spleen cell cultures was heat stable (56° for 30 min) and was destroyed by trypsin digestion. Thus, a chemotactic factor for macrophages, similar to a lymphocyte-derived chemotactic factor obtained in vitro, is present in vivo at the site of a cell-mediated immune reaction.

L5 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN

1974:424087 Document No. 81:24087 In vitro studies of a chemotactic lymphokine in the guinea pig. Wahl, Sharon M.; Altman, Leonard C.; Oppenheim, Joost J.; Mergenhagen, Stephan E. (Natl. Inst. Dent. Res., Natl. Inst. Health, Bethesda, MD, USA). International Archives of Allergy and Applied Immunology, 46(5), 768-84 (English) 1974. CODEN: IAAAAM.

ISSN: 0020-5915.
AB Lymphocytes from guinea pigs with delayed cutaneous reactivity to dinitrophenyl ovalbumin (DNP-OA) when challenged with this antigen in vitro elaborated a small mol. weight mediator which is chemotactic for monocytes. The in vitro production of mononuclear leukocyte (MNL) chemotactic factor (**CTX**) was carrier specific and correlated with delayed hypersensitivity. Production of this lymphokine by specific antigen or mitogen-stimulated spleen cells occurred within 8-24 hr of incubation, preceding measurable lymphocyte proliferation. MNL **CTX** was sensitive to proteases from C5 and other guinea pig lymphokines.

=> s EtxB
L6 272 ETXB

=> s l6 and allergy
L7 1 L6 AND ALLERGY

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L7 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2005 ACS on STN
1999:451202 Document No. 131:82960 **EtxB** or ganglioside GM1 for treating allergic or hypersensitivity conditions. Williams, Neil Andrew; Hirst, Timothy Raymond; Bienenstock, John (Oratol Limited, UK). PCT Int. Appl. WO 9934817 A1 19990715, 46 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-GB70 19990108. PRIORITY: GB 1998-487 19980109.
AB The use of an agent in the manufacture of a medicament to treat an allergic condition and/or a hypersensitivity condition is described. The agent is capable of modulating a ganglioside-associated activity. The agent is not coupled to an antigen. The modulation of the ganglioside-associated activity affects an allergic condition and/or a hypersensitivity condition. Examples of such modulators include ganglioside GM1 and E. coli enterotoxin B subunit.

=> s CtxB
L8 445 CTXB

=> s l8 and allergy
L9 1 L8 AND ALLERGY

=> d l9 cbib abs

L9 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2005 ACS on STN
2000:814337 Document No. 133:361908 Bacteriophage isolated from bacterial genomes and extrachromosomal elements and methods of use thereof. Karaolis, David K. R. (University of Maryland, Baltimore, USA). PCT Int. Appl. WO 2000067784 A1 20001116, 59 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US12580 20000510. PRIORITY: US 1999-PV133373 19990510.
AB The present invention relates to compns., methods, processes, etc.,

relating to bacteriophage which are encoded by chromosome, plasmids, or an extrachromosomal element of bacteria. The bacteriophage of the present invention are preferably encoded by pathogenicity islands in chromosomes or plasmids of pathogenic bacteria. The bacteriophage can be utilized as a pharmaceutical composition, e.g., to elicit an immune response, e.g., for the purpose of producing antibodies, as vaccines and vaccine vectors to regulate the immune system, e.g., for the prevention and treatment of **allergy**, disease, and other pathol. conditions. The invention finds addnl. utility in systems and methods for the detection of pathogens comprising bacteriophage and a system and method for the environmental eradication of pathogenic microorganisms.

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L10       9684 (WILLIAMS N?/AU OR HIRST T?/AU OR BIENENSTOCK J?/AU)

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L11        481 L10 AND TOXIN

=> s l11 and allergy
L12          2 L11 AND ALLERGY

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L13          2 DUP REMOVE L12 (0 DUPLICATES REMOVED)

=> d l13 1-2 cbib abs

L13  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2005 ACS on STN
1999:451202  Document No. 131:82960  EtxB or ganglioside GM1 for treating
     allergic or hypersensitivity conditions.  Williams, Neil Andrew;
     Hirst, Timothy Raymond; Bienenstock, John (Oratol
     Limited, UK).  PCT Int. Appl.  WO 9934817 A1 19990715, 46 pp.  DESIGNATED
     STATES: W:  AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,
     DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
     KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO,
     NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US,
     UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW:  AT, BE, BF, BJ,
     CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC,
     ML, MR, NE, NL, PT, SE, SN, TD, TG.  (English).  CODEN:  PIXXD2.
     APPLICATION:  WO 1999-GB70 19990108.  PRIORITY:  GB 1998-487 19980109.
AB   The use of an agent in the manufacture of a medicament to treat an allergic
     condition and/or a hypersensitivity condition is described.  The agent is
     capable of modulating a ganglioside-associated activity.  The agent is not
     coupled to an antigen.  The modulation of the ganglioside-associated activity
     affects an allergic condition and/or a hypersensitivity condition.
     Examples of such modulators include ganglioside GM1 and E. coli
     enterotoxin B subunit.

L13  ANSWER 2 OF 2  CAPLUS  COPYRIGHT 2005 ACS on STN
1994:694772  Document No. 121:294772  Pertussis toxin stimulates
     hypersensitivity and enhances nerve-mediated antigen uptake in rat
     intestine.  Kosecka, U.; Marshall, J. S.; Crowe, S. E.; Bienenstock,
     J.; Perdue, M. H. (Dep. Pathol., McMaster Univ., Hamilton, ON, L8N
     3Z5, Can.).  American Journal of Physiology, 267(5, Pt. 1), G745-G753
     (English) 1994.  CODEN:  AJPHAP.  ISSN:  0002-9513.  Publisher:  American
     Physiological Society.
AB   Sensitization of Sprague-Dawley rats by i.p. injection of recombinant
     wild-type pertussis toxin (wPT) plus ovalbumin (Ova) enhanced
     intestinal responses (at day 14:  .apprx.20-fold for luminal antigen,
     .apprx.2.5-fold for serosal antigen) compared with rats sensitized by
     injection of Ova alone.  In contrast, sensitization with an enzymically
     inactive mutant pertussis toxin (mPT, different in two amino
     acids) produced no significant effect.  Ova-specific IgE and IgG2a
     antibodies and greater nos. of mucosal mast cells were documented in
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wPT-sensitized rats. In addition, the short-circuit current (Isc) response to elec. transmural stimulation of nerves in intestinal prepns. was significantly augmented. Neurotoxin inhibited the secretory response to luminal but not serosal antigen. Immunophysiol. stimulation by wPT was still evident 8 mo postsensitization. Our studies indicate that pertussis **toxin** causes long-lasting hypersensitivity to coadministered antigens, involving increased production of reaginic antibodies, hyperplasia of mucosal mast cells, and enhanced neurally mediated uptake of antigen across the intestinal epithelium. These findings suggest a potential role for bacterial products in the development of immunophysiol. reactions to ingested antigens.

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L14 182 DUP REMOVE L11 (299 DUPLICATES REMOVED)

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L15 35 L14 AND "GM1"

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PROCESSING COMPLETED FOR L15
L16 35 DUP REMOVE L15 (0 DUPLICATES REMOVED)

=> d l16 1-35 cbib abs

L16 ANSWER 1 OF 35 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
2004:1045693 The Genuine Article (R) Number: 874MZ. Trafficking of exogenous peptides into proteasome-dependent major histocompatibility complex class I pathway following enterotoxin B subunit-mediated delivery. Hearn A R; de Haan L; Pemberton A J; **Hirst T R**; Rivett A J (Reprint). Univ Bristol, Sch Med Sci, Dept Biochem, Univ Walk, Bristol BS8 1TD, Avon, England (Reprint); Univ Bristol, Sch Med Sci, Dept Biochem, Bristol BS8 1TD, Avon, England; Univ Bristol, Sch Med Sci, Dept Pathol & Microbiol, Bristol BS8 1TD, Avon, England. j.rivett@bris.ac.uk. JOURNAL OF BIOLOGICAL CHEMISTRY (3 DEC 2004) Vol. 279, No. 49, pp. 51315-51322. ISSN: 0021-9258. Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3996 USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB The B-subunit component of Escherichia coli heat-labile enterotoxin (EtxB), which binds to cell surface **GM1** ganglioside receptors, was recently shown to be a highly effective vehicle for delivery of conjugated peptides into the major histocompatibility complex (MHC) class I pathway. In this study we have investigated the pathway of epitope delivery. The peptides used contained the epitope either located at the C terminus or with a C-terminal extension. Pretreatment of cells with cholesterol-disrupting agents blocked transport of EtxB conjugates to the Golgi/endoplasmic reticulum, but did not affect EtxB-mediated MHC class I presentation. Under these conditions, EtxB conjugates entered EEA1-positive early endosomes where peptides were cleaved and translocated into the cytosol. Endosome acidification was required for epitope presentation. Purified 20 S immunoproteasomes were able to generate the epitope from peptides in vitro, but 26 S proteasomes were not. Only presentation from the C-terminal extended peptide was proteasome-dependent in cells, and this was found to be significantly slower than presentation from peptides with the epitope at the C terminus. These results implicate the proteasome in the generation of the correct C terminus of the epitope and are consistent with proteasome-independent N-terminal trimming. Epitope presentation was blocked in a TAP-deficient cell line, providing further evidence that conjugated peptides enter the cytosol as well as demonstrating a requirement for the peptide transporter. Our findings demonstrate the utility of EtxB-mediated peptide delivery for rapid and efficient loading of MHC class I epitopes in several different cell types. Conjugated peptides are released from early endosomes into the cytosol

where they gain access to proteasomes and TAP in the "classical" pathway of class I presentation.

L16 ANSWER 2 OF 35 MEDLINE on STN

2004474715. PubMed ID: 15385486. The B subunit of Escherichia coli heat-labile enterotoxin induces both caspase-dependent and -independent cell death pathways in CD8+ T cells. Salmond Robert J; Williams Rachel; **Hirst Timothy R; Williams Neil A.** (Department of Pathology and Microbiology, School of Medical Sciences, University of Bristol, Bristol, United Kingdom.) Infection and immunity, (2004 Oct) 72 (10) 5850-7. Journal code: 0246127. ISSN: 0019-9567. Pub. country: United States. Language: English.

AB The nontoxic B subunit of Escherichia coli heat-labile enterotoxin (EtxB) is a potent immunomodulatory molecule that acts both as an adjuvant and to stimulate immune deviation processes, resulting in the suppression of Th1-associated inflammatory responses. The ability of EtxB to alter immune reactivity is dependent on its ability to modulate immune cell function through binding to cell surface molecules, the principal receptor of which is the ubiquitous **GM1**-ganglioside. EtxB activates B cells and antigen-presenting cells and induces the selective apoptosis of murine CD8+ T cells. We postulated that these effects are mediated by the induction of intracellular signaling pathways following EtxB-receptor interaction. We have previously shown that CD8+ T-cell apoptosis induced by EtxB results from the activation of the transcription factor NF-kappaB and caspases. Here we report that while caspase activity is required for apoptosis, additional features of cell death are caspase independent. EtxB induces a rapid loss of mitochondrial membrane potential and cell viability that are unaffected by caspase inhibitors. In addition, our data suggest that these processes are independent of the activity of Bax and Bcl-2 but are mediated by nitric oxide synthase.

L16 ANSWER 3 OF 35 MEDLINE on STN

2003084109. PubMed ID: 12595472. Mutant Escherichia coli heat-labile **toxin** B subunit that separates toxoid-mediated signaling and immunomodulatory action from trafficking and delivery functions. Fraser Sylvia A; de Haan Lolke; Hearn Arron R; Bone Heather K; Salmond Robert J; Rivett A Jennifer; **Williams Neil A; Hirst Timothy R.** (Department of Pathology & Microbiology, School of Medical Sciences, University of Bristol, University Walk, Bristol BS8 1TD, United Kingdom.) Infection and immunity, (2003 Mar) 71 (3) 1527-37. Journal code: 0246127. ISSN: 0019-9567. Pub. country: United States. Language: English.

AB The homopentameric B-subunit components of Escherichia coli heat-labile enterotoxin (EtxB) and cholera **toxin** (CtxB) possess the capacity to enter mammalian cells and to activate cell-signaling events in leukocytes that modulate immune cell function. Both properties have been attributed to the ability of the B subunits to bind to **GM1** -ganglioside receptors, a ubiquitous glycosphingolipid found in the plasma membrane. Here we describe the properties of EtxB(H57S), a mutant B subunit with a His-->Ser substitution at position 57. The mutant was found to be severely defective in inducing leukocyte signaling, as shown by failure to (i) trigger caspase 3-mediated CD8(+)-T-cell apoptosis, (ii) activate nuclear translocation of NF-kappaB in Jurkat T cells, (iii) induce a potent anti-B-subunit response in mice, or (iv) serve as a mucosal adjuvant. However, its **GM1** binding, cellular uptake, and delivery functions remained intact. This was further validated by the finding that EtxB(H57S) was as effective as EtxB in delivering a conjugated model class I epitope into the major histocompatibility complex class I pathway of a dendritic cell line. These observations imply that **GM1** binding alone is not sufficient to trigger the signaling events responsible for the potent immunomodulatory properties of EtxB. Moreover, they demonstrate that its signaling properties play no role in EtxB uptake and trafficking. Thus, EtxB(H57S) represents a novel tool for evaluating the complex cellular interactions and signaling events occurring after receptor interaction, as well as offering an alternative means of delivering attached peptides in the absence of the potent

immunomodulatory signals induced by wild-type B subunits.

L16 ANSWER 4 OF 35 MEDLINE on STN
2003551488. PubMed ID: 14630342. Ganglioside **GM1** binding **toxins** and human neuropathy-associated IgM antibodies differentially promote neuritogenesis in a PC12 assay. O'Hanlon Graham M; **Hirst Timothy R**; Willison Hugh J. (University Department of Neurology, Institute of Neurological Sciences, Southern General Hospital, Glasgow G51 4TF, Scotland, UK.) Neuroscience research, (2003 Dec) 47 (4) 383-90. Journal code: 8500749. ISSN: 0168-0102. Pub. country: Ireland. Language: English.

AB PC12 cells undergo neuritogenesis upon nerve growth factor (NGF) activation of the TrkA receptor, an effect mimicked by the ganglioside **GM1** binding B-subunit of cholera **toxin** (CTB). Modulation of neuritogenesis by a **GM1** ligand indicates a possible pathway for pathophysiological actions of neuropathy-associated anti-**GM1** antibodies. Here we examine the ability of **GM1** binding **toxins** and antibodies to induce neuritogenesis, using a PC12 neurite outgrowth assay. Cholera **toxin** (CT) and commercially prepared CTB (sCTB, contaminated with traces of the adenyl cyclase activating CT A-subunit) were highly neuritogenic. Recombinant cholera **toxin** B-subunit (rCTB, free from CTA) induced a much smaller effect, suggesting that the potent effects of sCTB are largely due to contaminating CTA. The recombinant **GM1** binding B-subunit of Escherichia coli heat-labile enterotoxin (rETxB) exhibited no neuritogenic activity, whilst rETx holotoxin, which activates adenyl cyclase, was highly neuritogenic. Monoclonal anti-**GM1** IgM antibodies from human neuropathy subjects induced small neuritogenic effects. These data indicate that **GM1**/ligand interaction does not necessarily lead to neuritogenesis and suggest that a specialisation of CTB, not shared by anti-**GM1** antibodies or rETxB, is required to activate TrkA. Our data also indicate that antibodies are unlikely to exert major modulatory effects on TrkA activity in patients with anti-**GM1** antibody-associated peripheral neuropathies.

L16 ANSWER 5 OF 35 MEDLINE on STN
2002253086. PubMed ID: 11877421. A kinetic model of intermediate formation during assembly of cholera **toxin** B-subunit pentamers. Lesieur Claire; Cliff Matthew J; Carter Rachel; James Roger F L; Clarke Anthony R; **Hirst Timothy R.** (Department of Pathology, School of Medical Sciences University of Bristol, Bristol, United Kingdom.) Journal of biological chemistry, (2002 May 10) 277 (19) 16697-704. Electronic Publication: 2002-03-04. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Cholera **toxin** is the most important virulence factor produced by Vibrio cholerae. The pentameric B-subunit of the **toxin** can bind to **GM1**-ganglioside receptors, leading to **toxin** entry into mammalian cells. Here, the in vitro disassembly and reassembly of CtxB(5) (the B subunit pentamer of cholera **toxin**) is investigated. When CtxB(5) was acidified at pH 1.0 and then neutralized, the B-subunits disassembled and could no longer migrate as SDS-stable pentamers on polyacrylamide gels or be captured by **GM1**. However, continued incubation at neutral pH resulted in the B-subunits regaining the capacity to be detected by **GM1** enzyme-linked immunosorbent assay (t(12) approximately 8 min) and to migrate as SDS-stable pentamers (t(12) approximately 15 min). Time-dependent changes in Trp fluorescence intensity during B-subunit reassembly occurred with a half-time of approximately 8 min, similar to that detected by **GM1** enzyme-linked immunosorbent assay, suggesting that both methods monitor earlier events than B-pentamer formation alone. Based on the Trp fluorescence intensity measurements, a kinetic model of the pathway of CtxB(5) reassembly was generated that depended on trans to cis isomerization of Pro-93 to give an interface capable of subunit-subunit interaction. The model suggests formation of intermediates in the reaction, and these were successfully detected by glutaraldehyde

cross-linking.

L16 ANSWER 6 OF 35 MEDLINE on STN

2002271835. PubMed ID: 12011020. Enhanced delivery of exogenous peptides into the class I antigen processing and presentation pathway. De Haan Lolke; Hearn Arron R; Rivett A Jennifer; **Hirst Timothy R.** (Department of Pathology & Microbiology, School of Medical Sciences, University of Bristol, Bristol BS8 1TD, United Kingdom.) Infection and immunity, (2002 Jun) 70 (6) 3249-58. Journal code: 0246127. ISSN: 0019-9567. Pub. country: United States. Language: English.

AB Current immunization strategies, using peptide or protein antigens, generally fail to elicit cytotoxic-T-lymphocyte responses, since these antigens are unable to access intracellular compartments where loading of major histocompatibility complex class I (MHC-I) molecules occurs. In an attempt to circumvent this, we investigated whether the **GM1** receptor-binding B subunit of Escherichia coli heat-labile **toxin** (EtxB) could be used to deliver class I epitopes. When a class I epitope was conjugated to EtxB, it was delivered into the MHC-I presentation pathway in a **GM1**-binding-dependent fashion and resulted in the appearance of MHC-I-epitope complexes at the cell surface. Importantly, we show that the efficiency of EtxB-mediated epitope delivery could be strikingly enhanced by incorporating, adjacent to the class I epitope, a 10-amino-acid segment from the C terminus of the DNA polymerase (Pol) of herpes simplex virus. The replacement of this 10-amino-acid segment by a heterologous sequence or the introduction of specific amino acid substitutions within this segment either abolished or markedly reduced the efficiency of class I epitope delivery. If the epitope was extended at its C terminus, EtxB-mediated delivery into the class I presentation pathway was found to be completely dependent on proteasome activity. Thus, by combining the **GM1**-targeting function of EtxB with the 10-amino-acid Pol segment, highly efficient delivery of exogenous epitopes into the endogenous pathway of class I antigen processing and presentation can be achieved.

L16 ANSWER 7 OF 35 MEDLINE on STN

2002158646. PubMed ID: 11890554. New insights into the structure-function relationships and therapeutic applications of cholera-like enterotoxins. **Hirst Timothy R**; Fraser Sylvia; Soriani Marco; Aman A Tholib; de Haan Lolke; Hearn Arron; Merritt Ethan. (Department of Pathology and Microbiology, University of Bristol, School of Medical Sciences, UK.. t.r.hirst@bristol.ac.uk) . International journal of medical microbiology : IJMM, (2002 Feb) 291 (6-7) 531-5. Ref: 41. Journal code: 100898849. ISSN: 1438-4221. Pub. country: Germany: Germany, Federal Republic of. Language: English.

AB Cholera **toxin** and E. coli heat-labile enterotoxin are structurally homologous proteins comprised of an enzymatically active A-subunit and five B-subunits that bind with high affinity to **GM1** -ganglioside receptors found on the surface of mammalian cells. The B-subunits have long been thought of simply as trafficking vehicles that trigger entry and subsequent delivery of the 'toxic' A-subunit into cells. Indeed, such is the capacity of the B-subunits to enter cells, that they have been developed as generic carriers for attachment and delivery of a variety of peptides into mammalian cells. However, the B-subunits also appear to possess discrete 'signalling functions', that induce both transcription factor and cell activation. These are thought to be directly responsible for the potent immunomodulatory properties of the B-subunits, and have resulted in their use as adjuvants and as agents to suppress inflammatory immune disorders. The relationship between the signalling properties of the B-subunits and their capacity to act as trafficking vehicles has remained unclear. In an effort to understand the structural requirements for these two functions, a set of mutant B-subunits, with amino acid substitutions at position His-57, have been generated and studied. Importantly, such mutant B-subunits retain an ability to bind with high affinity to **GM1** and to traffic into cells, but have entirely lost their capacity to activate immune cell

populations. Thus, while binding via **GM1** appears to be sufficient to trigger cellular uptake it is not sufficient to activate signal transduction. The His-57 region is therefore speculated to be actively engaged in triggering signalling events, possibly via cognate interaction with other cell surface molecules.

L16 ANSWER 8 OF 35 MEDLINE on STN
2002357108. PubMed ID: 12100719. Modulation of human monocytes by Escherichia coli heat-labile enterotoxin B-subunit; altered cytokine production and its functional consequences. Turcanu Victor; **Hirst Timothy R**; **Williams Neil A.** (University of Bristol, Department of Pathology and Microbiology, School of Medical Sciences, UK.) Immunology, (2002 Jul) 106 (3) 316-25. Journal code: 0374672. ISSN: 0019-2805. Pub. country: England: United Kingdom. Language: English.
AB In murine systems, the B subunit of Escherichia coli heat-labile enterotoxin (EtxB) is a potent immunomodulator capable of suppressing Th1-mediated autoimmune diseases. This results from its ability to bind cell surface receptors, principally **GM1**-ganglioside, and as a consequence down-regulate the pathological T helper type 1 (Th1) response. The capacity of EtxB to alter human T-cell responses has not been investigated. Here we show that EtxB, but not the receptor non-binding mutant EtxB (G33D), triggers the release of interleukin (IL)-10, IL-6 and tumour necrosis factor-alpha (TNF-alpha) by human monocytes. The production of IL-8, transforming growth factor-beta (TGF-beta) or IL-12 was not enhanced by EtxB. Indeed, EtxB was shown to inhibit IL-12 secretion in monocytes stimulated with interferon-gamma (IFN-gamma) and lipopolysaccharide (LPS) by an IL-10-independent mechanism. When EtxB-treated monocytes were used as antigen presenting cells in an allogeneic mixed lymphocyte reaction (MLR), IL-10 and IFN-gamma production were increased in comparison to levels seen in cultures stimulated with untreated monocytes; proliferation was unaltered. This modulation of the T-cell response was not only evident in the primary MLR triggered by EtxB-treated monocytes, but also upon restimulation of the responding T cells with fresh untreated monocytes; indicating that presentation by EtxB-treated monocytes leads to altered T-cell differentiation. Sorting experiments showed that IL-10 secreting T cells from the MLR cultures were strong suppressors of T-cell proliferation following their addition into a fresh primary MLR.

L16 ANSWER 9 OF 35 CAPLUS COPYRIGHT 2005 ACS on STN
2001:798749 Document No. 135:339267 Therapeutic agents. **Williams, Neil Andrew**; **Hirst, Timothy Raymond**; Nashar, Toufic Osman (UK). U.S. Pat. Appl. Publ. US 20010036917 A1 20011101, 53 pp., Cont.-in-part of U.S. 6,287,563. (English). CODEN: USXXCO. APPLICATION: US 2001-867914 20010530. PRIORITY: GB 1995-13733 19950705; US 1997-999458 19971229.
AB A method of treating diabetes in a mammalian subject by administering an agent capable of modulating a ganglioside GM-1 (GM-1) associated activity in an amount effect to treat the disease; wherein agent is selected from the group consisting of cholera **toxin** (Ctx), enterotoxins (Etx), the B subunit of Ctx and the B subunit of Etx, mutants and derivs. thereof. along with co-administration of antigens which are not so linked to form a single active agent.

L16 ANSWER 10 OF 35 MEDLINE on STN
2001419634. PubMed ID: 11447291. A mutant cholera **toxin** B subunit that binds **GM1**- ganglioside but lacks immunomodulatory or toxic activity. Aman A T; Fraser S; Merritt E A; Rodigherio C; Kenny M; Ahn M; Hol W G; **Williams N A**; Lencer W I; **Hirst T R.** (Department of Pathology and Microbiology, University of Bristol, Bristol BS81TD, United Kingdom.) Proceedings of the National Academy of Sciences of the United States of America, (2001 Jul 17) 98 (15) 8536-41. Electronic Publication: 2001-07-10. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.
AB **GM1**-ganglioside receptor binding by the B subunit of cholera **toxin** (CtxB) is widely accepted to initiate **toxin** action

by triggering uptake and delivery of the **toxin** A subunit into cells. More recently, **GM1** binding by isolated CtxB, or the related B subunit of Escherichia coli heat-labile enterotoxin (EtxB), has been found to modulate leukocyte function, resulting in the down-regulation of proinflammatory immune responses that cause autoimmune disorders such as rheumatoid arthritis and diabetes. Here, we demonstrate that **GM1** binding, contrary to expectation, is not sufficient to initiate **toxin** action. We report the engineering and crystallographic structure of a mutant cholera **toxin**, with a His to Ala substitution in the B subunit at position 57. Whereas the mutant retained pentameric stability and high affinity binding to **GM1** -ganglioside, it had lost its immunomodulatory activity and, when part of the holotoxin complex, exhibited ablated toxicity. The implications of these findings on the mode of action of cholera **toxin** are discussed.

L16 ANSWER 11 OF 35 CAPLUS COPYRIGHT 2005 ACS on STN
2000:175834 Document No. 132:217136 Peptide fragments of cholera **toxin** B or enterotoxin B as immunomodulators and vaccine adjuvants and for the treatment of **toxin**-induced diarrhea. **Williams, Neil Andrew**; **Hirst, Timothy Raymond** (University of Bristol, UK). PCT Int. Appl. WO 2000014114 A1 20000316, 62 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-GB2970 19990907. PRIORITY: GB 1998-19484 19980907.
AB A substance is provided which comprises any one or more of an amino acid sequence EVPGSQH, or a variant, homolog, fragment, derivative, or mimetic thereof. The substance is capable of acting in a manner that is the same as or is similar to enterotoxin B and/or cholera **toxin** B, but does not exhibit GM-1 binding activity. The substance may be used as an immunomodulator or vaccine adjuvant or for the treatment of **toxin** -induced diarrhea.

L16 ANSWER 12 OF 35 MEDLINE on STN
20012217 54. PubMed ID: 11111918. Floating cholera **toxin** into epithelial cells: functional association with caveolae-like detergent-insoluble membrane microdomains. Badizadegan K; Wolf A A; Rodighiero C; Jobling M; **Hirst T R**; Holmes R K; Lencer W I. (GI Cell Biology, Children's Hospital, Department of Pediatrics, Harvard Medical School, Harvard Digestive Diseases Center, Boston, MA 02115, USA.) International journal of medical microbiology : IJMM, (2000 Oct) 290 (4-5) 403-8. Ref: 38. Journal code: 100898849. ISSN: 1438-4221. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.
AB In polarized cells, signal transduction by cholera **toxin** (CT) requires apical endocytosis and retrograde transport into Golgi cisternae and likely endoplasmic reticulum (ER) (Lencer et al., J. Cell Biol. 131, 951-962 (1995)). We have recently found that the **toxin**'s apical membrane receptor ganglioside **GM1** acts specifically in this signal transduction pathway, likely by coupling CT with caveolae or caveolae-related membrane domains (lipid rafts) (Wolf et al., J. Cell Biol. 141, 917-927 (1998)). Work in progress shows that 1) cholesterol depletion uncouples the CT-**GM1** receptor complex from signal transduction, a characteristic of lipid rafts; 2) the **GM1** acyl chains rather than the carbohydrate head groups appear to account for the structural basis of ganglioside specificity in **toxin** trafficking; and 3) intestinal epithelial cells obtained from normal adult humans exhibit lipid rafts which differentiate between CT-**GM1** and LTIIb-GD1a complexes and which contain caveolin 1.

L16 ANSWER 13 OF 35 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on

STN
2001:82982 Document No.: PREV200100082982. Immunomodulation of the human MLR by E. coli-heat-labile **toxin** B subunit (EtxB): Induction of regulatory T cells. Turcanu, Victor [Reprint author]; **Williams, Neil A.** [Reprint author]. Dept. Pathology and Microbiology, University of Bristol, Bristol, BS8 1TD, UK. Immunology, (December, 2000) Vol. 101, No. Supplement 1, pp. 59. print.
Meeting Info.: Annual Congress of the British Society for Immunology. Harrogate, UK. December 05-08, 2000. British Society for Immunology.
CODEN: IMMUAM. ISSN: 0019-2805. Language: English.

L16 ANSWER 14 OF 35 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
2001:82909 Document No.: PREV200100082909. The role of **GM1** binding in mediating the activities of cholera **toxin**, E. coli heat labile enterotoxin and their respective B subunits. Fraser, S. A. [Reprint author]; Rodighiero, C. [Reprint author]; Aman, A. T. [Reprint author]; **Williams, N. A.** [Reprint author]; **Hirst, T. R.** [Reprint author]. Dept. of Pathology and Microbiology, University of Bristol, Bristol, BS8 1TD, UK. Immunology, (December, 2000) Vol. 101, No. Supplement 1, pp. 33. print.
Meeting Info.: Annual Congress of the British Society for Immunology. Harrogate, UK. December 05-08, 2000. British Society for Immunology.
CODEN: IMMUAM. ISSN: 0019-2805. Language: English.

L16 ANSWER 15 OF 35 CAPLUS COPYRIGHT 2005 ACS on STN
1999:736498 Document No. 131:335799 Immunomodulatory activity of B subunits of cholera **toxin**, verotoxin, and heat-labile enterotoxin.
Hirst, Timothy Raymond; Williams, Neil Andrew
(University of Bristol, UK). PCT Int. Appl. WO 9958145 A2 19991118, 63 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-GB1461 19990510. PRIORITY: GB 1998-9958 19980508; GB 1998-11954 19980603; GB 1998-12316 19980608.
AB The authors disclose the use of: (i) heat-labile enterotoxin B subunit (EtxB), cholera **toxin** B subunit (CtxB) or verotoxin B subunit (VtxB) in vaccine prepns. to alter the immune response to pathogens. In one example, the secretory IgA response to herpes virus glycoproteins is enhanced by the adjuvant activity of EtxB. In addition, the authors disclose the use of agents other than EtxB or CtxB, which have ganglioside **GM1**-binding activity, or an agent other than VtxB which has globotriosylceramide (Gb3)-binding activity for affecting intracellular signaling events.

L16 ANSWER 16 OF 35 CAPLUS COPYRIGHT 2005 ACS on STN
1999:451202 Document No. 131:82960 EtxB or ganglioside **GM1** for treating allergic or hypersensitivity conditions. **Williams, Neil Andrew; Hirst, Timothy Raymond; Bienenstock, John**
(Oratol Limited, UK). PCT Int. Appl. WO 9934817 A1 19990715, 46 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-GB70 19990108. PRIORITY: GB 1998-487 19980109.
AB The use of an agent in the manufacture of a medicament to treat an allergic condition and/or a hypersensitivity condition is described. The agent is capable of modulating a ganglioside-associated activity. The agent is not

coupled to an antigen. The modulation of the ganglioside-associated activity affects an allergic condition and/or a hypersensitivity condition. Examples of such modulators include ganglioside **GM1** and E. coli enterotoxin B subunit.

L16 ANSWER 17 OF 35 MEDLINE on STN
1999326151. PubMed ID: 10395933. Membrane traffic and the cellular uptake of cholera **toxin.** Lencer W I; **Hirst T R**; Holmes R K. (Combined Program in Pediatric Gastroenterology, Children's Hospital, Harvard Medical School, Harvard Digestive Diseases Center, Boston, MA, USA.. lencer@a1.tch.harvard.edu) . Biochimica et biophysica acta, (1999 Jul 8) 1450 (3) 177-90. Ref: 158. Journal code: 0217513. ISSN: 0006-3002. Pub. country: Netherlands. Language: English.
AB In nature, cholera **toxin** (CT) and the structurally related E. coli heat labile **toxin** type I (LTI) must breech the epithelial barrier of the intestine to cause the massive diarrhea seen in cholera. This requires endocytosis of **toxin**-receptor complexes into the apical endosome, retrograde transport into Golgi cisternae or endoplasmic reticulum (ER), and finally transport of **toxin** across the cell to its site of action on the basolateral membrane. Targeting into this pathway depends on **toxin** binding ganglioside **GM1** and association with caveolae-like membrane domains. Thus to cause disease, both CT and LTI co-opt the molecular machinery used by the host cell to sort, move, and organize their cellular membranes and substituent components.

L16 ANSWER 18 OF 35 CAPLUS COPYRIGHT 2005 ACS on STN
1997:181160 Document No. 126:170385 Therapeutic agents and autoimmune diseases. **Williams, Neil Andrew; Hirst, Timothy Raymond** ; Nashar, Toufic Osman (University of Bristol, UK). PCT Int. Appl. WO 9702045 A1 19970123, 62 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1996-GB1614 19960705. PRIORITY: GB 1995-13733 19950705.
AB There is disclosed the use, as an agent in the treatment or the prevention of an autoimmune disease, of: (i) an agent having GM-1 binding activity, other than Ctx or Etx, or the B subunits of Ctx and Etx; or (ii) an agent having an effect on GM-1 mediated intracellular signalling events, but no GM-1 binding activity. These agents may also be used in the treatment of human T cell leukemia, in the prevention of transplant rejection or GVHD or in a vaccination method for vaccinating a mammalian subject.

L16 ANSWER 19 OF 35 MEDLINE on STN
97289759. PubMed ID: 9144230. Prevention of autoimmune disease due to lymphocyte modulation by the B-subunit of Escherichia coli heat-labile enterotoxin. **Williams N A**; Stasiuk L M; Nashar T O; Richards C M; Lang A K; Day M J; **Hirst T R.** (Department of Pathology and Microbiology, School of Medical Sciences, University of Bristol, Bristol BS8 1TD, United Kingdom.) Proceedings of the National Academy of Sciences of the United States of America, (1997 May 13) 94 (10) 5290-5. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.
AB We demonstrate that the receptor binding moiety of Escherichia coli heat-labile enterotoxin (EtxB) can completely prevent autoimmune disease in a murine model of arthritis. Injection of male DBA/1 mice at the base of the tail with type II collagen in the presence of complete Freund's adjuvant normally leads to arthritis, as evidenced by inflammatory infiltration and swelling of the joints. A separate injection of EtxB at the same time as collagen challenge prevented leukocyte infiltration, synovial hyperplasia, and degeneration of the articular cartilage and reduced clinical symptoms of disease by 82%. The principle biological property of EtxB is its ability to bind to the ubiquitous cell surface

receptor **GM1** ganglioside, and to other galactose-containing glycolipids and galactoproteins. The importance of receptor interaction in mediating protection from arthritis was demonstrated by the failure of a non-receptor-binding mutant of EtxB to elicit any protective effect. Analysis of T cell responses to collagen, in cultures of draining lymph node cells, revealed that protection was associated with a marked increase in interleukin 4 production concomitant with a reduction in interferon gamma levels. Furthermore, in protected mice there was a significant reduction in anti-collagen antibody levels as well as an increase in the IgG1/IgG2a ratio. These observations show that protection is associated with a shift in the Th1/Th2 balance as well as a general reduction in the extent of the anti-type II collagen immune response. This suggests that EtxB-receptor-mediated modulation of lymphocyte responses provides a means of preventing autoimmune disease.

L16 ANSWER 20 OF 35 MEDLINE on STN

97376625. PubMed ID: 9232653. Structural studies of receptor binding by cholera **toxin** mutants. Merritt E A; Sarfaty S; Jobling M G; Chang T; Holmes R K; **Hirst T R**; Hol W G. (Department of Biological Structure, University of Washington, Seattle 98195-7742, USA.) Protein science : a publication of the Protein Society, (1997 Jul) 6 (7) 1516-28. Journal code: 9211750. ISSN: 0961-8368. Pub. country: United States. Language: English.

AB The wide range of receptor binding affinities reported to result from mutations at residue Gly 33 of the cholera **toxin** B-pentamer (CTB) has been most puzzling. For instance, introduction of an aspartate at this position abolishes receptor binding, whereas substitution by arginine retains receptor affinity despite the larger side chain. We now report the structure determination and 2.3-A refinement of the CTB mutant Gly 33-->Arg complexed with the **GM1** oligosaccharide, as well as the 2.2-A refinement of a Gly 33-->Asp mutant of the closely related Escherichia coli heat-labile enterotoxin B-pentamer (LTB). Two of the five receptor binding sites in the Gly 33-->Arg CTB mutant are occupied by bound **GM1** oligosaccharide; two other sites are involved in a reciprocal **toxin**:**toxin** interaction; one site is unoccupied. We further report a higher resolution (2.0 A) determination and refinement of the wild-type CTB:**GM1** oligosaccharide complex in which all five oligosaccharides are seen to be bound in essentially identical conformations. Saccharide conformation and binding interactions are very similar in both the CTB wild-type and Gly 33-->Arg mutant complexes. The protein conformation observed for the binding-deficient Gly 33-->Asp mutant of LTB does not differ substantially from that seen in the **toxin**:saccharide complexes. The critical nature of the side chain of residue 33 is apparently due to a limited range of subtle rearrangements available to both the **toxin** and the saccharide to accommodate receptor binding. The intermolecular interactions seen in the CTB (Gly 33-->Arg) complex with oligosaccharide suggest that the affinity of this mutant for the receptor is close to the self-affinity corresponding to the **toxin**:**toxin** binding interaction that has now been observed in crystal structures of three CTB mutants.

L16 ANSWER 21 OF 35 MEDLINE on STN

1998018503. PubMed ID: 9378497. Modulation of B-cell activation by the B subunit of Escherichia coli enterotoxin: receptor interaction up-regulates MHC class II, B7, CD40, CD25 and ICAM-1. Nashar T O; **Hirst T R**; **Williams N A.** (School of Medical Sciences, University of Bristol, UK.) Immunology, (1997 Aug) 91 (4) 572-8. Journal code: 0374672. ISSN: 0019-2805. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The B subunits of cholera **toxin** (CtxB) and Escherichia coli heat-labile enterotoxin (EtxB) are non-toxic lectins that bind and cross-link a ubiquitous cell glycolipid receptor, ganglioside **GM1** , and are recognized as potent mucosal and systemic immunogens. Here we examine the role of EtxB receptor occupancy in modulating the activation of B cells, in vitro, in primary lymphocyte cultures containing B and T cells. When 48-hr spleen cell cultures containing EtxB were compared with

those in the presence of a non-receptor binding mutant, EtxB(G33D), a marked shift in the ratio of CD4+ T cells: B cells was noted. Evidence suggested that this was the result of either enhanced survival or proliferation of B cells associated with receptor occupancy by EtxB. Investigation revealed that EtxB induced only a minimal increase in proliferation above that of EtxB(G33D), in mixed cell cultures, and failed to induce any cell division of purified B cells or T cells. In contrast, receptor-binding by EtxB markedly up-regulated the expression of major histocompatability complex (MHC) class II, B7, intracellular adhesion molecule-1 (ICAM-1), CD40 and CD25 on the B-cell surface. These results indicate that the polyclonal effects of EtxB on B cells are not associated with wide-scale proliferation, but more likely with maintenance of B-cell survival by activation of molecules essential for B-cell differentiation. The findings also highlight the essential role of **GM1** -interaction with EtxB in the regulation of lymphocyte responses.

L16 ANSWER 22 OF 35 MEDLINE on STN

97159760. PubMed ID: 9007276. Unexpected carbohydrate cross-binding by Escherichia coli heat-labile enterotoxin. Recognition of human and rabbit target cell glycoconjugates in comparison with cholera **toxin.** Karlsson K A; Teneberg S; Angstrom J; Kjellberg A; **Hirst T R**; Berstrom J; Miller-Podraza H. (Department of Medical Biochemistry, Goteborg University, Sweden.) Bioorganic & medicinal chemistry, (1996 Nov) 4 (11) 1919-28. Journal code: 9413298. ISSN: 0968-0896. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The bacterial protein enterotoxins, cholera **toxin** (CT) of Vibrio cholerae and heat-labile **toxin** (LT) of Escherichia coli, induce diarrhea by enhancing the secretory activity of the small intestine of man and rabbit (animal model). This physiological effect is mediated by **toxin** binding to a glycolipid receptor, the ganglioside **GM1**, Gal beta 3GalNAc beta 4(NeuAc alpha 3)GAl beta 4Glc beta 1Cer. However, LT, but not CT, was recently shown by us to bind also to paragloboside, Gal beta 4GlcNAc beta 3Gal beta 4Glc beta 1Cer, identified in the target cells. By molecular modeling of this tetrasaccharide in the known binding site of LT, the saccharide-peptide interaction was shown to be limited to the terminal disaccharide (N-acetyllactosamine). This sequence is expressed in many glycoconjugates, and we have therefore assayed glycolipids and glycoproteins prepared from the target tissues. In addition to paragloboside, receptor activity for LT was detected in glycoproteins of human origin and in polyglycosylceramides of rabbit. However, CT bound only to **GM1.** Two variants of LT with slightly different sequences, human (hLT) and porcine (pLT), were identical in their binding to target glycoproteins and polyglycosylceramides, but different regarding paragloboside, which was positive for pLT but negative for hLT. This difference is discussed on basis of modeling, taking in view the difference at position 13, with Arg in pLT and His in hLT. Although N-acetyllactosamine is differently recognized in form of paragloboside by the two **toxin** variants, we speculate that this sequence in human glycoproteins and rabbit polyglycosylceramides is the basis for the common binding. Much work remains, however, to clear up up this unexpected sophistication in target recognition.

L16 ANSWER 23 OF 35 MEDLINE on STN

97027223. PubMed ID: 8873387. Construction, purification and immunogenicity of antigen-antibody-LTB complexes. Green E A; Botting C; Webb H M; **Hirst T R**; Randall R E. (School of Biological and Medical Sciences, University of St. Andrews, Fife, UK.) Vaccine, (1996 Jul) 14 (10) 949-58. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB An oligonucleotide, encoding a short epitope peptide tag, termed Pk, was inserted at the 3'-end of the gene coding B-subunit of Escherichia coli heat-labile enterotoxin (LTB). The presence of the Pk epitope on LTB-Pk was used to construct novel macromolecular assemblies comprising LTB-Pk, an anti-Pk mAb, (mAb SV5-P-k) and Pk-linked recombinant SIV proteins. The 1:1:1 stoichiometry of such complexes was ensured by binding LTB-Pk to one

arm of mAb SV5-P-k and an SIV-Pk antigen to the other arm of the antibody. Such SIV-mAb-LTB macromolecular complexes bound to **GM1** -ganglioside in vitro, and when immunized systemically into mice were highly immunogenic, inducing both humoral and cell-mediated responses to the recombinant SIV antigens.

L16 ANSWER 24 OF 35 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

1996:408881 The Genuine Article (R) Number: UN188. Cross-linking of cell surface ganglioside **GM1** induces the selective apoptosis of mature CD8(+) T lymphocytes. Nashar T O (Reprint); **Williams N A** ; **Hirst T R.** UNIV KENT, RES SCH BIOSCI, CANTERBURY CT2 7NJ, KENT, ENGLAND (Reprint); UNIV BRISTOL, SCH MED SCI, DEPT PATHOL & MICROBIOL, BRISTOL BS8 1TD, AVON, ENGLAND. INTERNATIONAL IMMUNOLOGY (MAY 1996) Vol. 8, No. 5, pp. 731-736. ISSN: 0953-8178. Publisher: OXFORD UNIV PRESS UNITED KINGDOM, WALTON ST JOURNALS DEPT, OXFORD, ENGLAND OX2 6DP. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Gangliosides are glycosphingolipids found ubiquitously on the surface of mammalian cells, They contain a ceramide tail that is inserted into the membrane and exposed carbohydrate and sialic acid moieties, The non-toxic B subunit oligomer (EtxB) of Escherichia coil heat-labile enterotoxin (Etx) is a potent immunogen in vivo and has profound modulatory effects on EtxB-primed lymphocytes in vitro, properties which are dependent on its ability to bind to **GM1** ganglioside receptors, Here, it is shown that cross-linking **GM1** by EtxB causes a differential effect on mature CD4(+) and CD8(+) T cells from lymph node cultures proliferating in response to an unrelated antigen, ovalbumin, Addition of EtxB to such cultures led to the complete depletion of CD8(+) T cells compared with enhanced activation of CD4(+) T cells [as measured by expression of CD25 (IL-2R alpha)]. By contrast, addition of a mutant EtxB, EtxB(G33D), which does not bind to **GM1**, failed to trigger CD8(+) T cell depletion, When EtxB was added to isolated non-immune CD8(+) lymphocytes rapid (12-18 h) alterations in nuclear morphology and the appearance of sub-G(0)/G(1) levels of DNA were induced; properties which are characteristic of cells undergoing apoptosis, EtxB(G33D) failed to trigger apoptosis, indicating that the induction of the apoptotic signal was dependent on the binding of **GM1**, These findings provide an insight into the potent immunogenicity and immunomodulatory properties of E. coil enterotoxins as well as heralding a novel method for the selective induction of apoptosis in mature CD8(+) T lymphocytes.

L16 ANSWER 25 OF 35 MEDLINE on STN

96074761. PubMed ID: 7490296. Targeting of cholera **toxin** and Escherichia coli heat labile **toxin** in polarized epithelia: role of COOH-terminal KDEL. Lencer W I; Constable C; Moe S; Jobling M G; Webb H M; Ruston S; Madara J L; **Hirst T R**; Holmes R K. (Combined Program in Pediatric Gastroenterology and Nutrition, Children's Hospital, Boston, Massachusetts 02115, USA.) Journal of cell biology, (1995 Nov) 131 (4) 951-62. Journal code: 0375356. ISSN: 0021-9525. Pub. country: United States. Language: English.

AB Vibrio cholerae and Escherichia coli heat labile **toxins** (CT and LT) elicit a secretory response from intestinal epithelia by binding apical receptors (ganglioside **GM1**) and subsequently activating basolateral effectors (adenylate cyclase). We have recently proposed that signal transduction in polarized cells may require transcytosis of **toxin**-containing membranes (Lencer, W. I., G. Strohmeier, S. Moe, S. L. Carlson, C. T. Constable, and J. L. Madara. 1995. Proc. Natl. Acad. Sci. USA. 92:10094-10098). Targeting of CT into this pathway depends initially on binding of **toxin** B subunits to **GM1** at the cell surface. The anatomical compartments in which subsequent steps of CT processing occur are less clearly defined. However, the enzymatically active A subunit of CT contains the ER retention signal KDEL (RDEL in LT). Thus if the KDEL motif were required for normal CT trafficking, movement of CT from the Golgi to ER would be

implied. To test this idea, recombinant wild-type (wt) and mutant CT and LT were prepared. The COOH-terminal KDEL sequence in CT was replaced by seven unrelated amino acids: LEDERAS. In LT, a single point mutation replacing leucine with valine in RDEL was made. Wt and mutant **toxins** displayed similar enzymatic activities and binding affinities to **GM1** immobilized on plastic. Biologic activity of recombinant **toxins** was assessed as a Cl- secretory response elicited from the polarized human epithelial cell line T84 using standard electrophysiologic techniques. Mutations in K(R)DEL of both CT and LT delayed the time course of **toxin**-induced Cl- secretion. At T1/2, dose dependencies for K(R)DEL-mutant **toxins** were increased > or = 10-fold. KDEL-mutants displayed differentially greater temperature sensitivity. In direct concordance with a slower rate of signal transduction. KDEL-mutants were trafficked to the basolateral membrane more slowly than wt CT (assessed by selective cell surface biotinylation as transcytosis of B subunit). Mutation in K(R)DEL had no effect on the rate of **toxin** endocytosis. These data provide evidence that CT and LT interact directly with endogenous KDEL-receptors and imply that both **toxins** may require retrograde movement through Golgi cisternae and ER for efficient and maximal biologic activity.

L16 ANSWER 26 OF 35 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

1995:246152 Document No.: PREV199598260452. Targeting of cholera **toxin** and E. coli labile **toxin** in polarized epithelia: Role of C-terminal K (R) del. Lencer, W. I. [Reprint author]; **Hirst, T.**; Jobling, M.; Madara, J. L.; Holmes, R.. Children's Hosp., Harvard Med. Sch., Boston, MA, USA. Gastroenterology, (1995) Vol. 108, No. 4 SUPPL., pp. A300.
Meeting Info.: 95th Annual Meeting of the American Gastroenterological Association and Digestive Disease Week. San Diego, California, USA. May 14-17, 1995.
CODEN: GASTAB. ISSN: 0016-5085. Language: English.

L16 ANSWER 27 OF 35 MEDLINE on STN

94377479. PubMed ID: 8090758. Specific inhibition of herpes virus replication by receptor-mediated entry of an antiviral peptide linked to Escherichia coli enterotoxin B subunit. Marcello A; Loregian A; Cross A; Marsden H; **Hirst T R**; Palu G. (Institute of Microbiology, University of Padova, Italy.) Proceedings of the National Academy of Sciences of the United States of America, (1994 Sep 13) 91 (19) 8994-8. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB Mimetic peptides capable of selectively disrupting protein-protein interactions represent potential therapeutic agents for inhibition of viral and cellular enzymes. This approach was first suggested by the observation that the peptide YAGAVVNDL, corresponding to the carboxyl-terminal 9 amino acids of the small subunit of ribonucleotide reductase of herpes simplex virus, specifically inhibited the viral enzyme in vitro. Evaluation and use of this peptide as a potential antiviral agent has, however, been thwarted by its failure to inhibit virus replication in vivo, presumably because the peptide is too large to enter eukaryotic cells unaided. Here, we show that the nontoxic B subunit of Escherichia coli heat-labile enterotoxin can be used as a recombinant carrier for the receptor-mediated delivery of YAGAVVNDL into virally infected cells. The resultant fusion protein specifically inhibited herpes simplex virus type 1 replication and ribonucleotide reductase activity in quiescent Vero cells. Preincubation of the fusion protein with soluble **GM1** ganglioside abolished this antiviral effect, indicating that receptor-mediated binding to the target cell is necessary for its activity. This provides direct evidence of the usefulness of carrier-mediated delivery to evaluate the intracellular efficacy of a putative antiviral peptide.

L16 ANSWER 28 OF 35 MEDLINE on STN

95210904. PubMed ID: 7696856. Comparison of the glycolipid-binding specificities of cholera **toxin** and porcine Escherichia coli heat-labile enterotoxin: identification of a receptor-active non-ganglioside glycolipid for the heat-labile **toxin** in infant rabbit small intestine. Teneberg S; **Hirst T R**; Angstrom J; Karlsson K A. (Department of Medical Biochemistry and Microbiology, Goteborg University, Sweden.) Glycoconjugate journal, (1994 Dec) 11 (6) 533-40. Journal code: 8603310. ISSN: 0282-0080. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The binding specificities of cholera **toxin** and Escherichia coli heat-labile enterotoxin were investigated by binding of 125I-labelled **toxins** to reference glycosphingolipids separated on thin-layer chromatograms and coated in microtitre wells. The binding of cholera **toxin** was restricted to the **GM1** ganglioside. The heat-labile **toxin** showed the highest affinity for **GM1** but also bound, though less strongly, to the GM2, GD2 and GD1b gangliosides and to the non-acid glycosphingolipids gangliotetraosylceramide and lactoneotetraosylceramide. The infant rabbit small intestine, a model system for diarrhoea induced by the **toxins**, was shown to contain two receptor-active glycosphingolipids for the heat-labile **toxin**, **GM1** ganglioside and lactoneotetraosylceramide, whereas only the **GM1** ganglioside was receptor-active for cholera **toxin.** Preliminary evidence was obtained, indicating that epithelial cells of human small intestine also contain lactoneotetraosylceramide and similar sequences. By computer-based molecular modelling, lactoneotetraosylceramide was docked into the active site of the heat-labile **toxin**, using the known crystal structure of the **toxin** in complex with lactose. Interactions which may explain the relatively high **toxin** affinity for this receptor were found.

L16 ANSWER 29 OF 35 MEDLINE on STN

93175125. PubMed ID: 8438620. Recombinant enterotoxins as vaccines against Escherichia coli-mediated diarrhoea. Aitken R; **Hirst T R.** (Department of Microbiology, University of Glasgow, UK.) Vaccine, (1993) 11 (2) 227-33. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB A fusion protein, comprising the B subunit of the heat-labile enterotoxin and a portion of the precursor to the heat-stable enterotoxin of Escherichia coli, has been created by recombinant genetic techniques. It is exported successfully to the bacterial periplasm and assembles into pentamers which retain the ability to bind to **GM1** ganglioside. Native **toxin** epitopes are displayed and the molecule can be easily purified from periplasmic extracts of cells expressing the gene fusion. Although the protein carries the natural sequence of the heat-stable enterotoxin, it is greatly attenuated in toxicity. Systemic immunization of mice or oral administration of the fusion elicits antibody responses against both classes of E. coli enterotoxin.

L16 ANSWER 30 OF 35 MEDLINE on STN

92140031. PubMed ID: 1779757. Targeting and assembly of an oligomeric bacterial enterotoxoid in the endoplasmic reticulum of Saccharomyces cerevisiae. Schonberger O; **Hirst T R**; Pines O. (Department of Molecular Biology, Hebrew University, Hadassah Medical School, Jerusalem, Israel.) Molecular microbiology, (1991 Nov) 5 (11) 2663-71. Journal code: 8712028. ISSN: 0950-382X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB A hybrid protein consisting of the Escherichia coli lipoprotein signal sequence attached to the mature sequence of the B subunit of heat-labile enterotoxin (Lipo-EtxB) was expressed in yeast and E. coli. Analyses of cell lysates from Saccharomyces cerevisiae and E. coli expressing the protein revealed that both organisms were able to assemble Lipo-EtxB into oligomers that were (i) stable in the presence of sodium dodecyl sulphate, (ii) resistant to proteinase K degradation, and (iii) able to bind to **GM1**-ganglioside receptors. Each of these properties are

characteristic of the wild-type B subunit pentamer produced in E. coli. Assembly of Lipo-EtxB was found to be unaffected in a sec18 mutant of S. cerevisiae, which possesses a temperature-sensitive defect in protein transport from the endoplasmic reticulum (ER) to the Golgi apparatus, but was found not to assemble in a sec53 mutant, which causes the misfolding of proteins targeted to the ER. A kar2-1 mutation with a defect in the yeast homologue of BiP caused an 18-fold reduction in Lipo-EtxB assembly at the non-permissive temperature in S. cerevisiae. However, introduction of the wild-type KAR2 gene on a plasmid into the kar2-1 mutant completely suppressed the inhibition of Lipo-EtxB assembly. This provides the first evidence that KAR2 facilitates the assembly of an oligomeric protein in yeast and thus implicates KAR2 as a 'molecular chaperone'. The possible mechanisms of enterotoxoid assembly in E. coli and S. cerevisiae are discussed.

L16 ANSWER 31 OF 35 CAPLUS COPYRIGHT 2005 ACS on STN
1991:56942 Document No. 114:56942 Heat-labile **toxin** B subunit fusion proteins for use in vaccines. **Hirst, Timothy Raymond**; Aitken, Rober (University of Leicester, UK). Eur. Pat. Appl. EP 372928 A2 19900613, 11 pp. DESIGNATED STATES: R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE. (English). CODEN: EPXXDW. APPLICATION: EP 1989-312713 19891206. PRIORITY: GB 1988-28523 19881207; GB 1989-13991 19890617.

AB Fusion proteins containing the ganglioside **GM1**-binding domain of the heat-labile enterotoxin of enterotoxigenic Escherichia coli are prepared for use as the antigenic component of vaccines. The binding of the fusion proteins to membranes via the ganglioside-binding domain makes these fusion proteins effective mucosal immunogens. Chimeric genes for this domain and the E. coli heat-stable enterotoxin was prepared and the fusion protein manufactured by expression of the gene in E. coli. The resulting protein formed a pentamer as expected for the heat-labile **toxin**, was recognized by antibodies to both **toxins**, and one form of the fusion protein (lacking the first 48 amino acids of the heat-stable **toxin**) was non-toxic in mice at 725 ng/animal. The fusion protein was antigenic in rabbits and raised antibodies to both **toxins** (no data)..

L16 ANSWER 32 OF 35 MEDLINE on STN
88297157. PubMed ID: 2841198. Hybrid enterotoxin LTA::STa proteins and their protection from degradation by in vivo association with B-subunits of Escherichia coli heat-labile enterotoxin. Sanchez J; **Hirst T R** ; Uhlin B E. (Department of Medical Microbiology, University of Goteborg, Sweden.) Gene, (1988 Apr 29) 64 (2) 265-75. Journal code: 7706761. ISSN: 0378-1119. Pub. country: Netherlands. Language: English.

AB Chimeric proteins exhibiting antigenic determinants of the heat-labile enterotoxin (LT) and heat-stable (STa) enterotoxins on the same molecule may provide a means to obtain immunoprophylactic and diagnostic reagents for Escherichia coli-caused diarrhea. We recently showed that fusion of two different lengths of the STa gene to the C end of the A-subunit of LT (LTA) results in LTA::STa fusion proteins as monitored by **GM1** -ELISA [Sanchez et al.: FEBS Lett. 208 (1986) 194-198]. Here we determine the approximate molecular size of the LTA::STa fusion proteins and provide further evidence of their hybrid nature by immunoblot analysis. Using this technique we also demonstrate that to obtain detectable amounts of these recombinant proteins it is essential to coexpress them with the respective B-subunit of LT (LTB). We propose that this dependence on coexpression reflects the association between the LTA::STa hybrids and LTB subunits. The resulting LTA::STa/LTB complexes were found in the E. coli periplasm. This indicated that the exported hybrids, once associated with LTB, were stabilized and formed molecules that behaved essentially as native LT. The protective effect exerted by the B-subunit might conceivably be extended to other LTA-derived hybrid proteins, thus allowing the fusion of other foreign peptides to LTA and their subsequent recovery in the same fashion.

L16 ANSWER 33 OF 35 MEDLINE on STN
88007397. PubMed ID: 2820934. Alterations at the carboxyl terminus change assembly and secretion properties of the B subunit of Escherichia coli heat-labile enterotoxin. Sandkvist M; **Hirst T R**; Bagdasarian M. (Institute for Applied Cell and Molecular Biology, Umea University, Sweden.) Journal of bacteriology, (1987 Oct) 169 (10) 4570-6. Journal code: 2985120R. ISSN: 0021-9193. Pub. country: United States. Language: English.

AB The gene encoding the B subunit of heat-labile enterotoxin (etxB) was mutated at its 3' end by targeted addition of random nucleotide sequences. Gene products from five mutated etxB genes, all of which were shown to encode B subunits with short carboxy-terminal amino acid extensions, were analyzed with respect to a range of functional and structural properties. One class of altered B subunits, exemplified by EtxB124 and EtxB138, which both have seven extra amino acid residues, were found to be specifically defective in their ability to stably associate with A subunits and form holotoxin. Other altered B subunits were less subtlely affected by extensions at their C termini and were, in addition to their failure to associate with A subunits, unable to translocate into the periplasm of Escherichia coli, to pentamerize, or to bind to **GM1** ganglioside. This suggests that the carboxy-terminal domain of EtxB mediates A subunit-B subunit interaction.

L16 ANSWER 34 OF 35 CAPLUS COPYRIGHT 2005 ACS on STN
1987:152796 Document No. 106:152796 Mechanisms of enterotoxin secretion from Escherichia coli and Vibrio cholerae. **Hirst, T. R.** (Dep. Med. Microbiol., Univ. Goeteborg, Goeteborg, Swed.). FEMS Symposium, 31(Protein-Carbohydr. Interact. Biol. Syst.), 415-22 (English) 1986. CODEN: FEMSDW. ISSN: 0163-9188.

AB A discussion is presented on the export and secretion of enterotoxins from V. cholerae and E. coli which are responsible for causing severe diarrheal disease in man and farm animals. V. cholerae Secretes a potent cholera enterotoxin comprised of five identical B subunits which bind to **GM1** ganglioside receptors and a single A subunit that catalyzes ADP-ribosylation of adenylate cyclase. Enterotoxinogenic E. coli produces a heat-labile enterotoxin (LT) which is similar in structure and function to cholera **toxin**. However, in contrast to cholera **toxin** , LT is only exported as far as the periplasmic space of the E. coli cell envelope.

L16 ANSWER 35 OF 35 MEDLINE on STN
87054579. PubMed ID: 2430831. Immunoactive chimeric ST-LT enterotoxins of Escherichia coli generated by in vitro gene fusion. Sanchez J; Uhlin B E; Grundstrom T; Holmgren J; **Hirst T R.** FEBS letters, (1986 Nov 24) 208 (2) 194-8. Journal code: 0155157. ISSN: 0014-5793. Pub. country: Netherlands. Language: English.

AB Two different lengths of the gene encoding Escherichia coli heat-stable **toxin** (STa) were fused to the carboxy end of the gene coding for the E. coli heat-labile **toxin** A-subunit (LTA). The hybrid genes directed expression of chimeric LTA-STa proteins. Association of these chimeras with native heat-labile **toxin** B-subunit (LTB) resulted in protein complexes that bound to **GM1** ganglioside and thereby could be assayed in a **GM1** ELISA. The complexes reacted with monoclonal antibodies against either LTA, LTB or STa indicating that the STa and LT epitopes remained immunologically intact after fusion. Genetically constructed chimeric proteins exhibiting LT and STa antigens on the same molecule may represent a promising approach to development of broadly protective immunoprophylactic agents and/or useful immunodiagnostic reagents for diarrhoeal diseases caused by enterotoxinogenic E. coli.

=> s allergy
L17 283986 ALLERGY

=> s l17 and treatment
L18 45018 L17 AND TREATMENT

=> s l18 and toxin
L19 493 L18 AND TOXIN

=> s l19 and enterotoxin
L20 20 L19 AND ENTEROTOXIN

=> dup remove l20
PROCESSING COMPLETED FOR L20
L21 20 DUP REMOVE L20 (0 DUPLICATES REMOVED)

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L21 ANSWER 1 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN
2005:177824 Document No. 142:278721 Thio-modified aptamers binding to DNA-binding proteins, their sequences and use in **treatment** of viral infections and in construction of vaccines, compositions and adjuvants for modulating immune responses. Gorenstein, David G.; Luxon, Bruce A.; Herzog, Norbert; Aronson, Judith F.; Beasley, David; Barret, Allan; Shope, Robert E.; Yang, Xian Bin (Board of Regents-the University of Texas System, USA). PCT Int. Appl. WO 2005018537 A2 20050303, 72 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US16246 20040520. PRIORITY: US 2003-2003/PV472888 20030523.

AB The invention provides thio-modified aptamers (thioaptamers) that bind to specific DNA-binding proteins and/or transcription factors. The invention relates that thioaptamers can contain one or more phosphorothioate or phosphorodithioate linkages. The invention also provides vaccines, compns. and adjuvants composed of said thioaptamers plus an antigen (live-attenuated or heat-inactivated), wherein said antigen may be a viral, bacterial, self and/or cancer antigen. The invention also relates that said thioaptamers can bind to DNA proteins and/or transcription factors selected from NF-κB, RBP-Jκ, AP-1, NF-IL6, SP-1, GRE and SRE, wherein some of said proteins are known to be involved in signaling of immune responses. The invention further provides for the use of said thioaptamers and/or said compns. in modifying an immune response to a said disclosed antigens, including innate, humoral and/or T-cell immunity. The invention further relates that thioaptamers can enhance the innate immune response by targeting the Toll-like receptor family in mammals. Still further, the invention provides for the use of said thioaptamers and/or said compns. in treating a hemorrhagic and/or neuropathol. viral infection. Finally, the invention provides the sequences for said thioaptamers. The invention presented composition and methods for making and using a combinatorial library to identify said modified thioaptamers.

L21 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN
2005:485575 Document No. 143:32218 Sustained-release biodegradable microcapsules for delivery of anti-infective agents in the **treatment** and prevention of infections. Setterstrom, Jean A.; Tice, Thomas R.; Jacob, Elliot; Reid, Robert H.; Van Hamont, John; Boedecker, Edgar C.; Jeyanthi, Ramassubbu; Friden, Phil; Roberts, F. Donald; McQueen, Charles E.; Bhattacharjee, Apurba; Cross, Alan; Sadoff, Jerald; Zollinger, Wendell (The United States of America as Represented by the Secretary of the Army, USA). U.S. US 6902743 B1 20050607, 167 pp., Cont.-in-part of U.S. Ser. No. 920,326. (English). CODEN: USXXAM. APPLICATION: US 1998-55505 19980406. PRIORITY: US 1995-446149 19950522;

US 1995-446148 19950522; US 1996-590973 19960124; US 1996-598874 19960209; US 1996-675895 19960705; US 1996-698896 19960816; US 1997-788734 19970123; US 1997-896197 19970717; US 1997-920326 19970821.

AB Novel burst-free, sustained release biocompatible and biodegradable microcapsules which can be programmed to release their active core for variable durations ranging from 1-100 days in an aqueous physiol. environment. The microcapsules are comprised of a core of polypeptide or other biol. active agent encapsulated in a matrix of poly(lactide/glycolide) copolymer having a molar composition of lactide/glycolide from 90/10 to 40/60, which may contain a pharmaceutically-acceptable adjuvant, as a blend of uncapped free carboxyl end group and end-capped forms ranging to ratios from 100/0 to 1/99.

L21 ANSWER 3 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN

2005:480874 Document No. 143:192085 Nasal exposure to staphylococcal **enterotoxin** enhances the development of allergic rhinitis in mice. Okano, M.; Hattori, H.; Yoshino, T.; Sugata, Y.; Yamamoto, M.; Fujiwara, T.; Satoskar, A. A.; Satoskar, A. R.; Nishizaki, K. (Departments of Otolaryngology-Head & Neck Surgery, Okayama University Graduate School of Medicine and Dentistry, Okayama, Japan). Clinical and Experimental Allergy, 35(4), 506-514 (English) 2005. CODEN: CLEAEN. ISSN: 0954-7894. Publisher: Blackwell Publishing Ltd..

AB Background Staphylococcal **enterotoxins** (SEs) appear to play a role in the pathogenesis of allergic disease. However, little is known whether the nasal exposure to SE affects the development of allergic rhinitis (AR). Objective We sought to determine the in vivo effect of nasal exposure to SE on the development of AR using mouse model. Methods BALB/c mice were intranasally sensitized with Schistosoma mansoni egg antigen (SmEA) in the presence or absence of staphylococcal **enterotoxin** B (SEB). Control mice were intranasally sensitized with either SEB or SmEA alone. The production of antigen-specific antibodies including IgE, nasal eosinophilia and cytokines by nasal mononuclear cells was compared among mice that had or had not received SEB **treatment.** Results Nasal exposure to SEB enhanced the development of AR in SmEA-sensitized mice, as manifested by SmEA-specific IgE production, nasal eosinophilia, and IL-4 and IL-5 production by nasal mononuclear cells after Ag challenge. This **treatment** also elicited IFN-γ production by SmEA-primed cells. In addition, these mice produced SEB-specific IgE whereas mice treated with SEB without SmEA sensitization did not produce SEB-specific IgE or demonstrate nasal eosinophilia. Conclusion These results suggest that the nasal exposure to SEB enhances susceptibility to AR although the exposure to SE solely does not induce AR.

L21 ANSWER 4 OF 20 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2005186973 EMBASE Mucosal immunity and vaccines. Holmgren J.; Czerkinsky C.. J. Holmgren, Dept. of Med. Microbiol./Immunol., Goteborg Univ. Vacc. Res. Institute, Goteborg University, SE-405 30 Goteborg, Sweden. jan.holmgren@microbio.gu.se. Nature Medicine Vol. 11, No. 4 SUPPL., pp. S45-S53 2005.
Refs: 100.
ISSN: 1078-8956. CODEN: NAMEFI
Pub. Country: United Kingdom. Language: English. Summary Language: English.

ED Entered STN: 20050519

AB There is currently great interest in developing mucosal vaccines against a variety of microbial pathogens. Mucosally induced tolerance also seems to be a promising form of immunomodulation for treating certain autoimmune diseases and **allergies.** Hers we review the properties of the mucosal immune system and discuss advances in the development of mucosal vaccines for protection against infections and for **treatment** of various inflammatory disorders.

L21 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN

2003:991374 Document No. 140:40879 Bifunctional CpG or oligo-/polynucleotide

and **toxin** or **enterotoxin** containing composition.
Holmgren, Jan; Harandi, Ali M. (Gotovax AB, Swed.). PCT Int. Appl. WO 2003103708 A1 20031218, 46 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-SE935 20030605. PRIORITY: SE 2002-1701 20020605; US 2002-2002/PV385588 20020605.

AB A bifunctional composition comprising an intracellularly effective immunomodulating nucleic acid component containing at least one immunostimulatory, immunoinhibitory, or immunomodulating motif and selected from a mononucleotide, a dinucleotide, an oligonucleotide or a polynucleotide with either a natural phosphodiester backbone or a modified backbone, optionally in combination with a specific antigen, in association with a protein binding to specific receptors on mammalian cell surfaces selected from the group consisting of cholera **toxin** (CT), the subunit B of CT (CTB), Escherichia coli heat-labile **enterotoxin** (LT), the subunit B of LT (LTB), and proteins or protein derivs. that react with antiserum to CT or LT, bind to GM1 ganglioside, ADP-ribosylates an acceptor protein, or give rise to accumulation of cAMP in target cells, and antibodies or other proteins which after binding to a specific cell surface component can be internalized into the cell, is described. The composition is useful for **treatment** of tumors, infections, graft rejections, immunosuppressive states, autoimmune diseases and **allergies**, and further with a specific antigen it is useful for immunoprophylaxis, immunotherapy or induction of tolerance, and for **treatment** ex vivo of an antigen-presenting cell for subsequent infusion into a mammal for vaccination or immunotherapy purposes.

L21 ANSWER 6 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN

2003:656800 Document No. 139:191423 Immune-modulating peptide made of S. aureus **enterotoxin** B. Neuber, Karsten (Agelab Pharma G.m.b.H., Germany). PCT Int. Appl. WO 2003068812 A2 20030821, 46 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (German). CODEN: PIXXD2. APPLICATION: WO 2003-EP1511 20030214. PRIORITY: DE 2002-10207734 20020215; DE 2002-10240866 20020904.

AB The invention relates particularly to peptides which are specifically capable of binding IgE antibodies and can be obtained from naturally occurring S. aureus **enterotoxin** B (SEB), for example. The immune-modulating properties thereof are substantially different from those of bacterial SEB. Surprisingly, the inventive peptides do not induce proliferation of T cells, as opposed to SEB. Due to their properties, said peptides are suitable for treating diseases that are characterized by an increased serum IgE level and/or an increased production of interferon gamma and for treating diseases that are characterized by an imbalance in the Th1 and Th2 cytokine response, e.g. atopic eczema, lupus erythematosus, Crohn's disease, multiple sclerosis, psoriasis, and rheumatoid arthritis.

L21 ANSWER 7 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN

2003:656581 Document No. 139:197370 Preparation of aryl ureas containing pyridine, quinoline and isoquinoline N-oxide functionality as kinase inhibitors. Dumas, Jacques; Scott, William J.; Riedl, Bernd (Bayer Corporation, USA). PCT Int. Appl. WO 2003068229 A1 20030821, 67 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ,

CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US4110 20030211. PRIORITY: US 2002-2002/PV354935 20020211.

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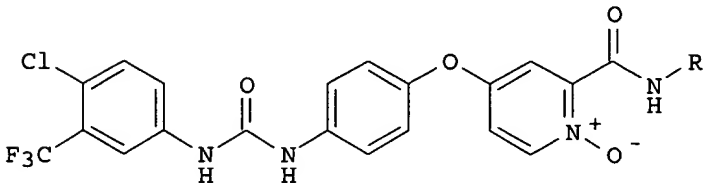

I

AB The title ureas containing a pyridine, quinoline, or isoquinoline functionality which is oxidized at the nitrogen heteroatom MLBNHCONHA [A = (un)substituted Ph, naphthyl, 5-6 membered monocyclic heteroaryl, 8-10 membered bicyclic heteroaryl; B = (un)substituted phenylene, naphthylene, 5-6 membered monocyclic heteroarylene, 8-10 membered bicyclic heteroarylene; L = (CH2)mO(CH2)l, (CH2)m(CH2)l, (CH2)mCO(CH2)l, etc.; m, l = 0-4; M = (un)substituted pyridine-1-oxide, quinoline-1-oxide, isoquinoline-1-oxide; with the provisos] which are useful in the **treatment** of (i) raf mediated diseases, for example, cancer, (ii) p38 mediated diseases such as inflammation and osteoporosis, and (iii) VEGF mediated diseases such as angiogenesis disorders, were claimed. Preparation of two ureas such as I [R = H, Me] which are not compds. of the invention, and have been distinguished from the compds. of the invention by a proviso, was described. Pharmaceutical composition comprising the title ureas was claimed.

L21 ANSWER 8 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN

2003:656580 Document No. 139:197369 Preparation of aryl ureas with angiogenesis inhibiting activity. Dumas, Jacques; Scott, William J.; Elting, James; Hatoum-Makdad, Holia (Bayer Corporation, USA). PCT Int. Appl. WO 2003068228 A1 20030821, 83 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US4103 20030211. PRIORITY: US 2002-PV354950 20020211.

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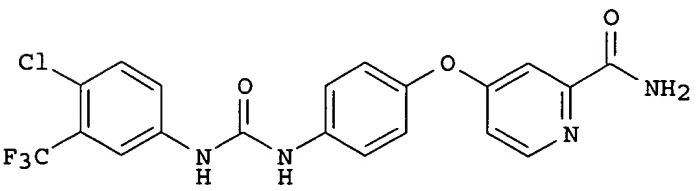

I

AB The title compds. ANHCONHB [A, B = (un)substituted Ph, naphthyl, 5-6

membered monocyclic heteroaryl, etc.], useful for treating diseases mediated by the VEGF induced signal transduction pathway characterized by abnormal angiogenesis or hyperpermeability processes, were claimed. Prepns. of three title ureas are described. E.g., a 3-step synthesis of the urea I (starting from Me 4-chloro-2-pyridinecarboxylate hydrochloride), was given. The KDR (VEGFR2) assay for testing the title ureas is described.

L21 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN
2003:633041 Document No. 139:178680 Compound and method for the prevention and/or the **treatment** of **allergy**. Saint-Remy, Jean-Marie; Jacquemin, Marc (Belg.). U.S. Pat. Appl. Publ. US 2003152581 A1 20030814, 26 pp., Cont.-in-part of U.S. 6,602,509. (English). CODEN: USXXCO. APPLICATION: US 2002-237656 20020910. PRIORITY: EP 1998-870167 19980730; US 1999-362731 19990729.
AB The present invention is related to a compound for the prevention and/or the **treatment** of **allergy** consisting of: at least one allergen antigenic determinant which is recognized by a B cell or an antibody secreted by a B cell of a non-atopic individual to said allergen, and at least one antigenic determinant of an antigen different from said allergen which triggers T cell activation.

L21 ANSWER 10 OF 20 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
2003192785 EMBASE Mucosal adjuvants and anti-infection and anti-immunopathology vaccines based on cholera **toxin**, cholera **toxin** B subunit and CpG DNA. Holmgren J.; Harandi A.M.; Czerkinsky C.. J. Holmgren, Department of Medical Microbiology, Goteborg Univ. Vacc. Res. Institute, Goteborg University, Guldhedsgatan 10A, SE-413 46 Goteborg, Sweden. jan.holmgren@microbio.gu.se. Expert Review of Vaccines Vol. 2, No. 2, pp. 205-217 2003.
Refs: 64.
ISSN: 1476-0584. CODEN: ERVXAX
Pub. Country: United Kingdom. Language: English. Summary Language: English.
ED Entered STN: 20030529
AB The mucosal immune system consists of an integrated network of lymphoid cells that work in concert with innate host factors to promote host defence. Mucosal immunization can be used both to protect the mucosal surfaces against colonization and invasion by microbial pathogens and to provide a means for immunological **treatment** of selected autoimmune, allergic or infectious-immunopathological disorders through the induction of antigen-specific tolerance. The development of mucosal vaccines, whether for prevention of infectious diseases or for oral tolerance immunotherapy, requires efficient antigen delivery and adjuvant systems. Significant progress has recently been made to generate partly or wholly detoxified derivatives of cholera **toxin** (including the completely nontoxic cholera **toxin** B subunit) and the closely related Escherichia coli heat-labile **enterotoxin**, with retained adjuvant activity. Cholera **toxin** B subunit is a protective component of a widely registered oral vaccine against cholera, and has proven to be a promising vector for either giving rise to anti-infective immunity or for inducing peripheral anti-inflammatory tolerance to chemically or genetically linked foreign antigens administered mucosally. Promising advances have also recently been made In the design of efficient mucosal adjuvants based on bacterial DNA that contains CpG-motifs and various imidazoquinoline compounds binding to different Toll-like receptors on mucosal antigen-presenting cells.

L21 ANSWER 11 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN
2002:142872 Document No. 136:211910 Human claudin 19, claudin 21 and claudin 22 which are associated with tight junctions, protein sequence and uses in therapy. Youakim, Adel; Dubose, Robert F.; Wiley, Steven R. (Immunex Corporation, USA). PCT Int. Appl. WO 2002014499 A2 20020221, 65 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ,

CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US25662 20010815. PRIORITY: US 2000-2000/PV22579U 20000815; US 2000-2000/PV225513 20000815.

AB The invention relates to new members of claudin polypeptide family, human claudin 19, claudin 21 and claudin 22. The invention provides an expression vector, host cells and methods for recombinant production of said claudins. The invention also relates to use of said said claudins in a methods for treating disorders related to tight junction formation and epithelial or endothelial barrier functions. The invention also relates to identification of agents that modulate said claudins polypeptide activities.

L21 ANSWER 12 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN

2002:409267 Document No. 137:6098 Heteroaryl ureas containing nitrogen hetero-atoms as p38 kinase inhibitors. Dumas, Jacques; Riedl, Bernd; Khire, Uday; Sibley, Robert N.; Hatoum-Mokdad, Holia; Monahan, Mary-katherine; Gunn, David E.; Lowinger, Timotthy B.; Scott, William J.; Smith, Roger A.; Wood, Jill E. (Bayer Corporation, USA). U.S. Pat. Appl. Publ. US 2002065296 A1 20020530, 39 pp., Cont.-in-part of U. S. Ser. No. 778,039. (English). CODEN: USXXCO. APPLICATION: US 2001-838286 20010420. PRIORITY: US 1999-PV115878 19990113; US 1999-257265 19990225; US 1999-425229 19991022; US 2001-778039 20010207.

AB This invention relates to the use of a group of heteroaryl ureas (I; for example, N-(2-methoxy-3-quinolyl)-N'-[4-[3-(N-methylcarbamoyl)phenoxy]phenyl]urea) containing N in treating p38 mediated diseases, and pharmaceutical compns. for use in such therapy. I is A-NHC(O)NH-B or a pharmaceutically acceptable salt thereof, wherein A is a substituted or unsubstituted pyridyl, quinolinyl or isoquinolinyl group, B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 50 C atoms with a cyclic structure bound directly to N, containing at least 5 cyclic members with 0-4 members of groups consisting of N, O and S. Information about the substituents for A and B are given in the claims. Although the methods of preparation are not claimed, 37 example prepns. are included as well as examples of preparation of intermediates. No pharmacol. data is included.

L21 ANSWER 13 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN

2000:104519 Document No. 132:165114 Compound and method for the prevention and/or the **treatment** of **allergy.** Saint-Remy, Jean-Marie; Jacquemin, Marc (UCB S. A., Belg.). PCT Int. Appl. WO 2000006694 A2 20000210, 50 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-BE92 19990720. PRIORITY: EP 1998-870167 19980730.

AB The present invention is related to a compound for the prevention and/or the **treatment** of **allergy** consisting of: at least one allergen antigenic determinant which is recognized by a B cell or an antibody secreted by a B cell of a non-atopic individual to said allergen, and at least one antigenic determinant of an antigen different from said allergen which triggers T cell activation. Thus, peptides or proteins containing T cell epitope of tetanus toxoid and/or B cell epitope of Der p II allergen, or polypeptide containing T cell epitope of influenza A virus and B cell epitope of Der p I allergen were prepared for administration by gene transfer technol. through adenoviral vehicle, or by oral through food

(e.g. acidified whey milk).

L21 ANSWER 14 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN
2000:15329 Document No. 132:61291 Methods of expanding and selecting disease associated T-cells using antigen-presenting cells and disease associated antigens. Kaltoft, Keld; Agnholt, Jorgen (Den.). PCT Int. Appl. WO 2000000587 A1 20000106, 124 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-DK363 19990625. PRIORITY: DK 1998-848 19980626; DK 1998-895 19980701; US 1998-91684 19980702.

AB Methods of expanding and selecting disease associated T-cells, continuous T-cell lines as well as T-cell lines obtainable by these methods are disclosed. Furthermore, pharmaceutical compns. and vaccines comprising activated disease associated T-cell are disclosed. The uses of the T-cell and T-cell lines are numerous and include methods of diagnosis, methods for the **treatment**, alleviation or prevention of diseases associated with activation of T-cells, methods of testing the effect of medicaments against T-cell associated diseases, methods of detecting T-cell growth factors, methods of monitoring the response to **treatment**, alleviation or prevention of diseases associated with activation of T-cells, and methods of identifying disease associated antigens. Peripheral blood mononuclear cells were cultured with IL-2 and IL-4 and allostimulated with Psor-2 cells, a T-cell line from a patient with psoriasis vulgaris.

L21 ANSWER 15 OF 20 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
2000:551436 The Genuine Article (R) Number: 334CP. Prolonged oral **treatment** with low doses of allergen conjugated to cholera **toxin** B subunit suppresses immunoglobulin E antibody responses in sensitized mice. Rask C; Holmgren J (Reprint); Fredriksson M; Lindblad M; Nordstrom I; Sun J B; Czerkinsky C. Gothenburg Univ, Dept Med Microbiol & Immunol, Guldhedsgatan 10, S-41346 Gothenburg, Sweden (Reprint); Gothenburg Univ, Dept Med Microbiol & Immunol, S-41346 Gothenburg, Sweden; Fac Med Pasteur, INSERM, U364, Nice, France. CLINICAL AND EXPERIMENTAL ALLERGY (JUL 2000) Vol. 30, No. 7, pp. 1024-1032. ISSN: 0954-7894. Publisher: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background Oral tolerance is a long recognized method for inducing systemic immunological tolerance. However, large doses of antigen and frequent administrations are often required. By linking the antigen to the nontoxic mucosa-binding B subunit of cholera **toxin** (CTB), the required amount can be dramatically reduced. We have previously shown that mucosal administration of small amounts of antigens coupled to CTB can suppress peripheral Th1 cell-reactivity and associated inflammatory immunopathology in both naive and systemically-immunized animals. Induction of oral tolerance by repeated feeding of relatively small doses of antigen has, in some cases been shown to involve the generation of regulatory Th2-like CD4(+) T cells, and hence could promote rather than suppress type I immunoglobulin (Ig) E-mediated allergic responses.

Objectives We examined whether oral prophylactic or therapeutic administration of a model allergen coupled to CTB would modulate allergen-specific IgE responses in high IgE responder Balb/c mice.

Methods Ovalbumin (OVA) was used as a model allergen. Mice were treated perorally with free or CTB-coupled OVA before or after systemic priming with alum-adsorbed OVA. Allergen-specific IgE levels in serum were measured with the passive cutaneous anaphylaxis test at various time-points.

Results Oral administration of a single low dose of CTB-linked OVA,

prior to systemic sensitization and challenge with OVA, suppressed allergen-specific serum IgE antibody responses. **Treatment** with comparable doses of free OVA was much less effective. Most importantly, oral **treatment** with CTB-OVA conjugate could also suppress an already initiated IgE antibody response, but to achieve such a 'therapeutic effect', administration of multiple low doses of conjugate over a long time was required. Oral **treatment** with CTB-OVA conjugate could also effectively suppress antigen-specific Th1-mediated delayed-type hypersensitivity. Thus **treatment** with a CTB-conjugated model allergen can affect a broad range of T-cell-driven immune responses, even in antigen-experienced animals.

Conclusion These results may impact on the development of therapeutic vaccines against type I **allergies.**

L21 ANSWER 16 OF 20 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

1999:772394 The Genuine Article (R) Number: 246TE. The modulation of B7.2 and B7.1 on B cells by immunosuppressive agents. Jirapongsananuruk O; Leung D Y M (Reprint). Natl Jewish Med & Res Ctr, Dept Paediat, 1400 Jackson St, Denver, CO 80206 USA (Reprint); Natl Jewish Med & Res Ctr, Dept Paediat, Denver, CO 80206 USA; Univ Colorado, Hlth Sci Ctr, Dept Paediat, Denver, CO USA. CLINICAL AND EXPERIMENTAL IMMUNOLOGY (OCT 1999) Vol. 118, No. 1, pp. 1-8. ISSN: 0009-9104. Publisher: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Several recent studies demonstrate that B7.2, but not B7.1, play an important role in allergic inflammation and IgE production. Agents that down-regulate B7.2 may therefore be of benefit for the **treatment** of Th2-driven allergic diseases. Our current study was carried our to investigate the effect of immunosuppressive agents, cyclosporin A (CsA) and dexamethasone, on B7.2 and B7.1 expression on B cells stimulated with the superantigen, toxic shock syndrome **toxin**-1 (TSST-1). The analysis of B7.2 and B7.1 on the same cells by flow cytometry demonstrated that TSST-1 up-regulated B7.2(+)B7.1(-) but not B7.1(+)B7.2(-) on B cells in a dose-dependent fashion. CsA and dexamethasone significantly downregulated B7.2(+)B7.1(-) but up-regulated B7.2(-)B7.1(+) B cells in the presence or absence of TSST-1 (100 ng/ml). Interestingly, the combination of CsA and dexamethasone was much more potent in the inhibition of B7.2 expression than either of these agents alone. As CD40 is known to up-regulate B7.2 expression on B cells, the mechanism of B7.2 down-regulation by CsA and dexamethasone was further studied by investigating the effect of these agents on CD40 expression on B cells. TSST-1 significantly increased CD40 expression on B cells. However, the addition of CsA or dexamethasone significantly down-regulated CD40 expression. Anti-CD40 MoAb significantly reversed the effects of CsA or dexamethasone on B7.2 and B7.1 expression, suggesting that T cell engagement of CD40 plays a role in the mechanisms by which CsA and dexamethasone acts on B cells. These data demonstrate the modulatory effect of CsA and dexamethasone on B7.2 and B7.1 expression on B cells and the potential role of CD40 in mediating this effect.

L21 ANSWER 17 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN

1995:271411 Document No. 122:53910 Inhibition of the development of immediate hypersensitivity by staphylococcal **enterotoxin** B. Saloga, Joachim; Lack, Gideon; Bradley, Kathrine; Renz, Harald; Larsen, Gary; Leung, Donald Y. M.; Gelfand, Erwin W. (Dep. Pediatrics, Natl. Jewish Cent. Immunology, Denver, CO, USA). European Journal of Immunology, 24(12), 3140-7 (English) 1994. CODEN: EJIMAF. ISSN: 0014-2980. Publisher: VCH.

AB The authors investigated the ability of staphylococcal **enterotoxin** B (SEB) to modify the immediate hypersensitivity response induced in BALB/c mice following sensitization to ovalbumin (OVA), a response mediated by OVA-reactive Vβ8 T cells. Mice were sensitized by skin painting with OVA every second day over a period of 2 wk. SEB, a potent activator of Vβ8+ T cells, was administered at the same site where

OVA was applied (skin of the lower abdomen) following two different protocols. In protocol (A) SEB was injected intradermally 1 day before painting with OVA and on day 7; in protocol B, SEB was injected each time OVA was applied to the skin (eight times). SEB (but not SEA) altered the development of immediate hypersensitivity to OVA, as demonstrated by the reduction in allergen-specific IgE, decreased OVA-specific immediate skin test responsiveness, and prevented the development of increased airway responsiveness after bronchial challenge with OVA. Injections of SEB did not alter the proliferative responses of local draining lymph node cells or spleen mononuclear cells to OVA, indicating that administration of SEB did not inhibit the sensitization to OVA, but shifted the immune response away from an immediate type response (IgE/IgG1) to IgG2a, IgG2b and IgG3. Although both protocols of SEB **treatment** did not lead to a major deletion of the Vβ8 T cell population, they did reduce the proliferative response of Vβ8+ T cells to OVA. These data indicate that the bacterial **toxin** SEB is capable of modifying the immediate hypersensitivity response induced by OVA by altering the functional capacity of antigen-reactive Vβ8 T cells.

L21 ANSWER 18 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN

1994:555532 Document No. 121:155532 The model of arthritis induced by superantigen in mice. Nagai, Hiroichi; Takaoka, Yuko; Kamada, Hiroyuki; Mori, Hiroshi (Dep. Pharmacology, Gifu Pharmaceutical Univ., Gifu, 502, Japan). Life Sciences, 55(12), PL233-PL237 (English) 1994. CODEN: LIFSAK. ISSN: 0024-3205.

AB S.c. injection of Staphylococcal **enterotoxin** B (SEB) produced by Staphylococcus aureus, caused severe arthritis in DBA/1J mice which had been previously immunized with bovine type II collagen. The severity of this arthritis was dose dependent and prolonged joint inflammation with erosion of bone was observed Anti-type II collagen antibodies were detected in the serum of arthritic mice. Effector T cells against type II collagen were also detected by delayed type hypersensitivity in the skin. Moreover, a significant decrease in the ratio between T cells and B cells and an increase in the ratio between CD4+ cells and CD8+ cells was observed in spleen cells from arthritic mice. Prednisolone suppresses the induction and development of clin. signs of arthritis in mice. This evidence suggests that this exptl. arthritis model may provide a means to examine the role of superantigens and the efficacy of pharmacol. agents for the **treatment** of rheumatoid arthritis.

L21 ANSWER 19 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN

1991:115084 Document No. 114:115084 Antiallergy agents containing allergens and adjuvants and antiallergy agents containing allergen-adjuvant complexes. Watanabe, Naohiro (Japan). Jpn. Kokai Tokkyo Koho JP 02235823 A2 19900918 Heisei, 5 pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 1989-54887 19890309.

AB Antiallergy agents, which are useful for **treatment** of type I **allergy**, e.g. asthma and allergic rhinitis, and have low toxicity, contain (1) allergens and adjuvants stimulating production of IgA against the allergens; or (2) allergens bonded with the adjuvants (via spacers). Nasal administration of 10 μg ovalbumin and 1.0 μg cholera **toxin** produced antiovalbumin IgA in mice, vs. none, without the **toxin.**

L21 ANSWER 20 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN

1987:634622 Document No. 107:234622 Cysteinyl leukotrienes as mediators of staphylococcal **enterotoxin** B in the monkey. Scheuber, P. H.; Denzlinger, C.; Wilker, D.; Beck, G.; Keppler, D.; Hammer, D. K. (Biochem. Inst., Univ. Freiburg, Freiburg, Fed. Rep. Ger.). European Journal of Clinical Investigation, 17(5), 455-9 (English) 1987. CODEN: EJCIB8. ISSN: 0014-2972.

AB The role of cysteinyl leukotrienes (LTs) in the action of staphylococcal **enterotoxin** B (SEB) was investigated in unsensitized monkeys using inhibitors of prostanoid synthesis and LT action and by measuring generation of LT in vivo. LY 171883, a selective LTD4/LTE4 receptor

antagonist, was highly efficient in inhibiting immediate-type hypersensitivity reactions in the skin and protecting against the emetic response provoked by SEB in a concentration-dependent manner. Inhibition of prostanoid formation by pretreatment of monkeys with indomethacin or aspirin did not influence SEB responses. Based on chromatog. and RIA, the generation of endogenous cysteinyl LTs was demonstrated in vivo. The concentration of LTE4, the major biliary cysteinyl LT detected, increased 10-fold
and a novel cysteinyl LT metabolite in urine indicated strongly enhanced LT generation upon challenge with SEB. Cysteinyl LTs are important mediators in the pathophysiol. of SEB-induced enteric intoxication. Therefore, cysteinyl LT antagonists may be of therapeutic value in the **treatment** of this intestinal disorder.

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FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 09:43:37 ON 13 SEP 2005

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L1           897 S ETX
L2             1 S L1 AND ALLERGY
L3         13688 S CTX
L4            14 S L3 AND ALLERGY
L5            13 DUP REMOVE L4 (1 DUPLICATE REMOVED)
L6           272 S ETXB
L7             1 S L6 AND ALLERGY
L8           445 S CTXB
L9             1 S L8 AND ALLERGY
L10         9684 S (WILLIAMS N?/AU OR HIRST T?/AU OR BIENENSTOCK J?/AU)
L11          481 S L10 AND TOXIN
L12            2 S L11 AND ALLERGY
L13            2 DUP REMOVE L12 (0 DUPLICATES REMOVED)
L14          182 DUP REMOVE L11 (299 DUPLICATES REMOVED)
L15           35 S L14 AND "GM1"
L16           35 DUP REMOVE L15 (0 DUPLICATES REMOVED)
L17       283986 S ALLERGY
L18        45018 S L17 AND TREATMENT
L19          493 S L18 AND TOXIN
L20           20 S L19 AND ENTEROTOXIN
L21           20 DUP REMOVE L20 (0 DUPLICATES REMOVED)

=> s l19 and enterotoxin
L22           20 L19 AND ENTEROTOXIN

=> dup remove l22
PROCESSING COMPLETED FOR L22
L23           20 DUP REMOVE L22 (0 DUPLICATES REMOVED)

=> d l23 1-20 cbib abs

L23  ANSWER 1 OF 20  CAPLUS  COPYRIGHT 2005 ACS on STN
2005:177824   Document No. 142:278721  Thio-modified aptamers binding to
     DNA-binding proteins, their sequences and use in treatment of
     viral infections and in construction of vaccines, compositions and
     adjuvants for modulating immune responses.  Gorenstein, David G.; Luxon,
     Bruce A.; Herzog, Norbert; Aronson, Judith F.; Beasley, David; Barret,
     Allan; Shope, Robert E.; Yang, Xian Bin (Board of Regents-the University
     of Texas System, USA).  PCT Int. Appl. WO 2005018537 A2 20050303, 72 pp.
     DESIGNATED STATES: W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY,
     BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB,
     GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
     LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM,
     PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT,
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TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US16246 20040520. PRIORITY: US 2003-2003/PV472888 20030523.

AB The invention provides thio-modified aptamers (thioaptamers) that bind to specific DNA-binding proteins and/or transcription factors. The invention relates that thioaptamers can contain one or more phosphorothioate or phosphorodithioate linkages. The invention also provides vaccines, compns. and adjuvants composed of said thioaptamers plus an antigen (live-attenuated or heat-inactivated), wherein said antigen may be a viral, bacterial, self and/or cancer antigen. The invention also relates that said thioaptamers can bind to DNA proteins and/or transcription factors selected from NF-κB, RBP-Jκ, AP-1, NF-IL6, SP-1, GRE and SRE, wherein some of said proteins are known to be involved in signaling of immune responses. The invention further provides for the use of said thioaptamers and/or said compns. in modifying an immune response to a said disclosed antigens, including innate, humoral and/or T-cell immunity. The invention further relates that thioaptamers can enhance the innate immune response by targeting the Toll-like receptor family in mammals. Still further, the invention provides for the use of said thioaptamers and/or said compns. in treating a hemorrhagic and/or neuropathol. viral infection. Finally, the invention provides the sequences for said thioaptamers. The invention presented composition and methods for making and using a combinatorial library to identify said modified thioaptamers.

L23 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN

2005:485575 Document No. 143:32218 Sustained-release biodegradable microcapsules for delivery of anti-infective agents in the **treatment** and prevention of infections. Setterstrom, Jean A.; Tice, Thomas R.; Jacob, Elliot; Reid, Robert H.; Van Hamont, John; Boedecker, Edgar C.; Jeyanthi, Ramassubbu; Friden, Phil; Roberts, F. Donald; McQueen, Charles E.; Bhattacharjee, Apurba; Cross, Alan; Sadoff, Jerald; Zollinger, Wendell (The United States of America as Represented by the Secretary of the Army, USA). U.S. US 6902743 B1 20050607, 167 pp., Cont.-in-part of U.S. Ser. No. 920,326. (English). CODEN: USXXAM. APPLICATION: US 1998-55505 19980406. PRIORITY: US 1995-446149 19950522; US 1995-446148 19950522; US 1996-590973 19960124; US 1996-598874 19960209; US 1996-675895 19960705; US 1996-698896 19960816; US 1997-788734 19970123; US 1997-896197 19970717; US 1997-920326 19970821.

AB Novel burst-free, sustained release biocompatible and biodegradable microcapsules which can be programmed to release their active core for variable durations ranging from 1-100 days in an aqueous physiol. environment. The microcapsules are comprised of a core of polypeptide or other biol. active agent encapsulated in a matrix of poly(lactide/glycolide) copolymer having a molar composition of lactide/glycolide from 90/10 to 40/60, which may contain a pharmaceutically-acceptable adjuvant, as a blend of uncapped free carboxyl end group and end-capped forms ranging to ratios from 100/0 to 1/99.

L23 ANSWER 3 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN

2005:480874 Document No. 143:192085 Nasal exposure to staphylococcal **enterotoxin** enhances the development of allergic rhinitis in mice. Okano, M.; Hattori, H.; Yoshino, T.; Sugata, Y.; Yamamoto, M.; Fujiwara, T.; Satoskar, A. A.; Satoskar, A. R.; Nishizaki, K. (Departments of Otolaryngology-Head & Neck Surgery, Okayama University Graduate School of Medicine and Dentistry, Okayama, Japan). Clinical and Experimental Allergy, 35(4), 506-514 (English) 2005. CODEN: CLEAEN. ISSN: 0954-7894. Publisher: Blackwell Publishing Ltd..

AB Background Staphylococcal **enterotoxins** (SEs) appear to play a role in the pathogenesis of allergic disease. However, little is known whether the nasal exposure to SE affects the development of allergic rhinitis (AR). Objective We sought to determine the in vivo effect of nasal exposure to SE on the development of AR using mouse model. Methods BALB/c mice were intranasally sensitized with Schistosoma mansoni egg antigen

(SmEA) in the presence or absence of staphylococcal **enterotoxin** B (SEB). Control mice were intranasally sensitized with either SEB or SmEA alone. The production of antigen-specific antibodies including IgE, nasal eosinophilia and cytokines by nasal mononuclear cells was compared among mice that had or had not received SEB **treatment.** Results Nasal exposure to SEB enhanced the development of AR in SmEA-sensitized mice, as manifested by SmEA-specific IgE production, nasal eosinophilia, and IL-4 and IL-5 production by nasal mononuclear cells after Ag challenge. This **treatment** also elicited IFN-γ production by SmEA-primed cells. In addition, these mice produced SEB-specific IgE whereas mice treated with SEB without SmEA sensitization did not produce SEB-specific IgE or demonstrate nasal eosinophilia. Conclusion These results suggest that the nasal exposure to SEB enhances susceptibility to AR although the exposure to SE solely does not induce AR.

L23 ANSWER 4 OF 20 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2005186973 EMBASE Mucosal immunity and vaccines. Holmgren J.; Czerkinsky C.. J. Holmgren, Dept. of Med. Microbiol./Immunol., Goteborg Univ. Vacc. Res. Institute, Goteborg University, SE-405 30 Goteborg, Sweden. jan.holmgren@microbio.gu.se. Nature Medicine Vol. 11, No. 4 SUPPL., pp. S45-S53 2005.
Refs: 100.
ISSN: 1078-8956. CODEN: NAMEFI
Pub. Country: United Kingdom. Language: English. Summary Language: English.

ED Entered STN: 20050519

AB There is currently great interest in developing mucosal vaccines against a variety of microbial pathogens. Mucosally induced tolerance also seems to be a promising form of immunomodulation for treating certain autoimmune diseases and **allergies.** Hers we review the properties of the mucosal immune system and discuss advances in the development of mucosal vaccines for protection against infections and for **treatment** of various inflammatory disorders.

L23 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN

2003:991374 Document No. 140:40879 Bifunctional CpG or oligo-/polynucleotide and **toxin** or **enterotoxin** containing composition.
Holmgren, Jan; Harandi, Ali M. (Gotovax AB, Swed.). PCT Int. Appl. WO 2003103708 A1 20031218, 46 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-SE935 20030605. PRIORITY: SE 2002-1701 20020605; US 2002-2002/PV385588 20020605.

AB A bifunctional composition comprising an intracellularly effective immunomodulating nucleic acid component containing at least one immunostimulatory, immunoinhibitory, or immunomodulating motif and selected from a mononucleotide, a dinucleotide, an oligonucleotide or a polynucleotide with either a natural phosphodiester backbone or a modified backbone, optionally in combination with a specific antigen, in association with a protein binding to specific receptors on mammalian cell surfaces selected from the group consisting of cholera **toxin** (CT), the subunit B of CT (CTB), Escherichia coli heat-labile **enterotoxin** (LT), the subunit B of LT (LTB), and proteins or protein derivs. that react with antiserum to CT or LT, bind to GM1 ganglioside, ADP-ribosylates an acceptor protein, or give rise to accumulation of cAMP in target cells, and antibodies or other proteins which after binding to a specific cell surface component can be internalized into the cell, is described. The composition is useful for **treatment** of tumors, infections, graft rejections, immunosuppressive states, autoimmune diseases and

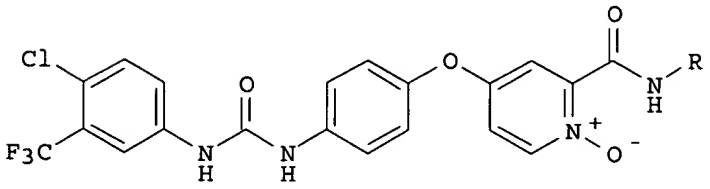
allergies, and further with a specific antigen it is useful for immunoprophylaxis, immunotherapy or induction of tolerance, and for **treatment** ex vivo of an antigen-presenting cell for subsequent infusion into a mammal for vaccination or immunotherapy purposes.

L23 ANSWER 6 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN
2003:656800 Document No. 139:191423 Immune-modulating peptide made of S. aureus **enterotoxin** B. Neuber, Karsten (Agelab Pharma G.m.b.H., Germany). PCT Int. Appl. WO 2003068812 A2 20030821, 46 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (German). CODEN: PIXXD2. APPLICATION: WO 2003-EP1511 20030214. PRIORITY: DE 2002-10207734 20020215; DE 2002-10240866 20020904.

AB The invention relates particularly to peptides which are specifically capable of binding IgE antibodies and can be obtained from naturally occurring S. aureus **enterotoxin** B (SEB), for example. The immune-modulating properties thereof are substantially different from those of bacterial SEB. Surprisingly, the inventive peptides do not induce proliferation of T cells, as opposed to SEB. Due to their properties, said peptides are suitable for treating diseases that are characterized by an increased serum IgE level and/or an increased production of interferon gamma and for treating diseases that are characterized by an imbalance in the Th1 and Th2 cytokine response, e.g. atopic eczema, lupus erythematosus, Crohn's disease, multiple sclerosis, psoriasis, and rheumatoid arthritis.

L23 ANSWER 7 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN
2003:656581 Document No. 139:197370 Preparation of aryl ureas containing pyridine, quinoline and isoquinoline N-oxide functionality as kinase inhibitors. Dumas, Jacques; Scott, William J.; Riedl, Bernd (Bayer Corporation, USA). PCT Int. Appl. WO 2003068229 A1 20030821, 67 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US4110 20030211. PRIORITY: US 2002-2002/PV354935 20020211.

GI



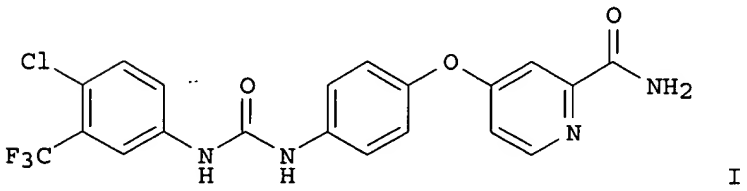
I

AB The title ureas containing a pyridine, quinoline, or isoquinoline functionality which is oxidized at the nitrogen heteroatom MLBNHCONHA [A = (un)substituted Ph, naphthyl, 5-6 membered monocyclic heteroaryl, 8-10 membered bicyclic heteroaryl; B = (un)substituted phenylene, naphthylene, 5-6 membered monocyclic heteroarylene, 8-10 membered bicyclic heteroarylene; L = (CH2)mO(CH2)l, (CH2)m(CH2)l, (CH2)mCO(CH2)l, etc.; m, l = 0-4; M = (un)substituted pyridine-1-oxide, quinoline-1-oxide,

isoquinoline-1-oxide; with the provisos] which are useful in the **treatment** of (i) raf mediated diseases, for example, cancer, (ii) p38 mediated diseases such as inflammation and osteoporosis, and (iii) VEGF mediated diseases such as angiogenesis disorders, were claimed. Preparation of two ureas such as I [R = H, Me] which are not compds. of the invention, and have been distinguished from the compds. of the invention by a proviso, was described. Pharmaceutical composition comprising the title ureas was claimed.

L23 ANSWER 8 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN
2003:656580 Document No. 139:197369 Preparation of aryl ureas with angiogenesis inhibiting activity. Dumas, Jacques; Scott, William J.; Elting, James; Hatoum-Makdad, Holia (Bayer Corporation, USA). PCT Int. Appl. WO 2003068228 A1 20030821, 83 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US4103 20030211. PRIORITY: US 2002-PV354950 20020211.

GI



I

AB The title compds. ANHCONHB [A, B = (un)substituted Ph, naphthyl, 5-6 membered monocyclic heteroaryl, etc.], useful for treating diseases mediated by the VEGF induced signal transduction pathway characterized by abnormal angiogenesis or hyperpermeability processes, were claimed. Prepns. of three title ureas are described. E.g., a 3-step synthesis of the urea I (starting from Me 4-chloro-2-pyridinecarboxylate hydrochloride), was given. The KDR (VEGFR2) assay for testing the title ureas is described.

L23 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN
2003:633041 Document No. 139:178680 Compound and method for the prevention and/or the **treatment** of **allergy.** Saint-Remy, Jean-Marie; Jacquemin, Marc (Belg.). U.S. Pat. Appl. Publ. US 2003152581 A1 20030814, 26 pp., Cont.-in-part of U.S. 6,602,509. (English). CODEN: USXXCO. APPLICATION: US 2002-237656 20020910. PRIORITY: EP 1998-870167 19980730; US 1999-362731 19990729.

AB The present invention is related to a compound for the prevention and/or the **treatment** of **allergy** consisting of: at least one allergen antigenic determinant which is recognized by a B cell or an antibody secreted by a B cell of a non-atopic individual to said allergen, and at least one antigenic determinant of an antigen different from said allergen which triggers T cell activation.

L23 ANSWER 10 OF 20 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
2003192785 EMBASE Mucosal adjuvants and anti-infection and anti-immunopathology vaccines based on cholera **toxin**, cholera **toxin** B subunit and CpG DNA. Holmgren J.; Harandi A.M.; Czerkinsky C.. J. Holmgren, Department of Medical Microbiology, Goteborg Univ. Vacc.

Res. Institute, Goteborg University, Guldhedsgatan 10A, SE-413 46 Goteborg, Sweden. jan.holmgren@microbio.gu.se. Expert Review of Vaccines Vol. 2, No. 2, pp. 205-217 2003.
Refs: 64.
ISSN: 1476-0584. CODEN: ERVXAX
Pub. Country: United Kingdom. Language: English. Summary Language: English.

ED Entered STN: 20030529

AB The mucosal immune system consists of an integrated network of lymphoid cells that work in concert with innate host factors to promote host defence. Mucosal immunization can be used both to protect the mucosal surfaces against colonization and invasion by microbial pathogens and to provide a means for immunological **treatment** of selected autoimmune, allergic or infectious-immunopathological disorders through the induction of antigen-specific tolerance. The development of mucosal vaccines, whether for prevention of infectious diseases or for oral tolerance immunotherapy, requires efficient antigen delivery and adjuvant systems. Significant progress has recently been made to generate partly or wholly detoxified derivatives of cholera **toxin** (including the completely nontoxic cholera **toxin** B subunit) and the closely related Escherichia coli heat-labile **enterotoxin**, with retained adjuvant activity. Cholera **toxin** B subunit is a protective component of a widely registered oral vaccine against cholera, and has proven to be a promising vector for either giving rise to anti-infective immunity or for inducing peripheral anti-inflammatory tolerance to chemically or genetically linked foreign antigens administered mucosally. Promising advances have also recently been made In the design of efficient mucosal adjuvants based on bacterial DNA that contains CpG-motifs and various imidazoquinoline compounds binding to different Toll-like receptors on mucosal antigen-presenting cells.

L23 ANSWER 11 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN

2002:142872 Document No. 136:211910 Human claudin 19, claudin 21 and claudin 22 which are associated with tight junctions, protein sequence and uses in therapy. Youakim, Adel; Dubose, Robert F.; Wiley, Steven R. (Immunex Corporation, USA). PCT Int. Appl. WO 2002014499 A2 20020221, 65 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM; AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US25662 20010815. PRIORITY: US 2000-2000/PV22579U 20000815; US 2000-2000/PV225513 20000815.

AB The invention relates to new members of claudin polypeptide family, human claudin 19, claudin 21 and claudin 22. The invention provides an expression vector, host cells and methods for recombinant production of said claudins. The invention also relates to use of said said claudins in a methods for treating disorders related to tight junction formation and epithelial or endothelial barrier functions. The invention also relates to identification of agents that modulate said claudins polypeptide activities.

L23 ANSWER 12 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN

2002:409267 Document No. 137:6098 Heteroaryl ureas containing nitrogen hetero-atoms as p38 kinase inhibitors. Dumas, Jacques; Riedl, Bernd; Khire, Uday; Sibley, Robert N.; Hatoum-Mokdad, Holia; Monahan, Mary-katherine; Gunn, David E.; Lowinger, Timotthy B.; Scott, William J.; Smith, Roger A.; Wood, Jill E. (Bayer Corporation, USA). U.S. Pat. Appl. Publ. US 2002065296 A1 20020530, 39 pp., Cont.-in-part of U. S. Ser. No. 778,039. (English). CODEN: USXXCO. APPLICATION: US 2001-838286 20010420. PRIORITY: US 1999-PV115878 19990113; US 1999-257265 19990225; US 1999-425229 19991022; US 2001-778039 20010207.

AB This invention relates to the use of a group of heteroaryl ureas (I; for example, N-(2-methoxy-3-quinolyl)-N'-[4-[3-(N-methylcarbamoyl)phenoxy]phenyl]urea) containing N in treating p38 mediated diseases, and pharmaceutical compns. for use in such therapy. I is A-NHC(O)NH-B or a pharmaceutically acceptable salt thereof, wherein A is a substituted or unsubstituted pyridyl, quinolinyl or isoquinolinyl group, B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 50 C atoms with a cyclic structure bound directly to N, containing at least 5 cyclic members with 0-4 members of groups consisting of N, O and S. Information about the substituents for A and B are given in the claims. Although the methods of preparation are not claimed, 37 example prepns. are included as well as examples of preparation of intermediates. No pharmacol. data is included.

L23 ANSWER 13 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN

2000:104519 Document No. 132:165114 Compound and method for the prevention and/or the **treatment** of **allergy**. Saint-Remy, Jean-Marie; Jacquemin, Marc (UCB S. A., Belg.). PCT Int. Appl. WO 2000006694 A2 20000210, 50 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-BE92 19990720. PRIORITY: EP 1998-870167 19980730.

AB The present invention is related to a compound for the prevention and/or the **treatment** of **allergy** consisting of: at least one allergen antigenic determinant which is recognized by a B cell or an antibody secreted by a B cell of a non-atopic individual to said allergen, and at least one antigenic determinant of an antigen different from said allergen which triggers T cell activation. Thus, peptides or proteins containing T cell epitope of tetanus toxoid and/or B cell epitope of Der p II allergen, or polypeptide containing T cell epitope of influenza A virus and B cell epitope of Der p I allergen were prepared for administration by gene transfer technol. through adenoviral vehicle, or by oral through food (e.g. acidified whey milk).

L23 ANSWER 14 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN

2000:15329 Document No. 132:61291 Methods of expanding and selecting disease associated T-cells using antigen-presenting cells and disease associated antigens. Kaltoft, Keld; Agnholt, Jorgen (Den.). PCT Int. Appl. WO 2000000587 A1 20000106, 124 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-DK363 19990625. PRIORITY: DK 1998-848 19980626; DK 1998-895 19980701; US 1998-91684 19980702.

AB Methods of expanding and selecting disease associated T-cells, continuous T-cell lines as well as T-cell lines obtainable by these methods are disclosed. Furthermore, pharmaceutical compns. and vaccines comprising activated disease associated T-cell are disclosed. The uses of the T-cell and T-cell lines are numerous and include methods of diagnosis, methods for the **treatment**, alleviation or prevention of diseases associated with activation of T-cells, methods of testing the effect of medicaments against T-cell associated diseases, methods of detecting T-cell growth factors, methods of monitoring the response to **treatment**, alleviation or prevention of diseases associated with activation of T-cells, and methods of identifying disease associated antigens. Peripheral blood mononuclear cells were cultured with IL-2 and IL-4 and allostimulated with

Psor-2 cells, a T-cell line from a patient with psoriasis vulgaris.

L23 ANSWER 15 OF 20 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

2000:551436 The Genuine Article (R) Number: 334CP. Prolonged oral **treatment** with low doses of allergen conjugated to cholera **toxin** B subunit suppresses immunoglobulin E antibody responses in sensitized mice. Rask C; Holmgren J (Reprint); Fredriksson M; Lindblad M; Nordstrom I; Sun J B; Czerkinsky C. Gothenburg Univ, Dept Med Microbiol & Immunol, Guldhedsgatan 10, S-41346 Gothenburg, Sweden (Reprint); Gothenburg Univ, Dept Med Microbiol & Immunol, S-41346 Gothenburg, Sweden; Fac Med Pasteur, INSERM, U364, Nice, France. CLINICAL AND EXPERIMENTAL ALLERGY (JUL 2000) Vol. 30, No. 7, pp. 1024-1032. ISSN: 0954-7894. Publisher: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background Oral tolerance is a long recognized method for inducing systemic immunological tolerance. However, large doses of antigen and frequent administrations are often required. By linking the antigen to the nontoxic mucosa-binding B subunit of cholera **toxin** (CTB), the required amount can be dramatically reduced. We have previously shown that mucosal administration of small amounts of antigens coupled to CTB can suppress peripheral Th1 cell-reactivity and associated inflammatory immunopathology in both naive and systemically-immunized animals. Induction of oral tolerance by repeated feeding of relatively small doses of antigen has, in some cases been shown to involve the generation of regulatory Th2-like CD4(+) T cells, and hence could promote rather than suppress type I immunoglobulin (Ig) E-mediated allergic responses.

Objectives We examined whether oral prophylactic or therapeutic administration of a model allergen coupled to CTB would modulate allergen-specific IgE responses in high IgE responder Balb/c mice.

Methods Ovalbumin (OVA) was used as a model allergen. Mice were treated perorally with free or CTB-coupled OVA before or after systemic priming with alum-adsorbed OVA. Allergen-specific IgE levels in serum were measured with the passive cutaneous anaphylaxis test at various time-points.

Results Oral administration of a single low dose of CTB-linked OVA, prior to systemic sensitization and challenge with OVA, suppressed allergen-specific serum IgE antibody responses. **Treatment** with comparable doses of free OVA was much less effective. Most importantly, oral **treatment** with CTB-OVA conjugate could also suppress an already initiated IgE antibody response, but to achieve such a 'therapeutic effect', administration of multiple low doses of conjugate over a long time was required. Oral **treatment** with CTB-OVA conjugate could also effectively suppress antigen-specific Th1-mediated delayed-type hypersensitivity. Thus **treatment** with a CTB-conjugated model allergen can affect a broad range of T-cell-driven immune responses, even in antigen-experienced animals.

Conclusion These results may impact on the development of therapeutic vaccines against type I **allergies.**

L23 ANSWER 16 OF 20 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

1999:772394 The Genuine Article (R) Number: 246TE. The modulation of B7.2 and B7.1 on B cells by immunosuppressive agents. Jirapongsananuruk O; Leung D Y M (Reprint). Natl Jewish Med & Res Ctr, Dept Paediat, 1400 Jackson St, Denver, CO 80206 USA (Reprint); Natl Jewish Med & Res Ctr, Dept Paediat, Denver, CO 80206 USA; Univ Colorado, Hlth Sci Ctr, Dept Paediat, Denver, CO USA. CLINICAL AND EXPERIMENTAL IMMUNOLOGY (OCT 1999) Vol. 118, No. 1, pp. 1-8. ISSN: 0009-9104. Publisher: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Several recent studies demonstrate that B7.2, but not B7.1, play an important role in allergic inflammation and IgE production. Agents that down-regulate B7.2 may therefore be of benefit for the **treatment**

of Th2-driven allergic diseases. Our current study was carried our to investigate the effect of immunosuppressive agents, cyclosporin A (CsA) and dexamethasone, on B7.2 and B7.1 expression on B cells stimulated with the superantigen, toxic shock syndrome **toxin**-1 (TSST-1). The analysis of B7.2 and B7.1 on the same cells by flow cytometry demonstrated that TSST-1 up-regulated B7.2(+)B7.1(-) but not B7.1(+)B7.2(-) on B cells in a dose-dependent fashion. CsA and dexamethasone significantly downregulated B7.2(+)B7.1(-) but up-regulated B7.2(-)B7.1(+) B cells in the presence or absence of TSST-1 (100 ng/ml). Interestingly, the combination of CsA and dexamethasone was much more potent in the inhibition of B7.2 expression than either of these agents alone. As CD40 is known to up-regulate B7.2 expression on B cells, the mechanism of B7.2 down-regulation by CsA and dexamethasone was further studied by investigating the effect of these agents on CD40 expression on B cells. TSST-1 significantly increased CD40 expression on B cells. However, the addition of CsA or dexamethasone significantly down-regulated CD40 expression. Anti-CD40 MoAb significantly reversed the effects of CsA or dexamethasone on B7.2 and B7.1 expression, suggesting that T cell engagement of CD40 plays a role in the mechanisms by which CsA and dexamethasone acts on B cells. These data demonstrate the modulatory effect of CsA and dexamethasone on B7.2 and B7.1 expression on B cells and the potential role of CD40 in mediating this effect.

L23 ANSWER 17 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN

1995:271411 Document No. 122:53910 Inhibition of the development of immediate hypersensitivity by staphylococcal **enterotoxin** B. Saloga, Joachim; Lack, Gideon; Bradley, Kathrine; Renz, Harald; Larsen, Gary; Leung, Donald Y. M.; Gelfand, Erwin W. (Dep. Pediatrics, Natl. Jewish Cent. Immunology, Denver, CO, USA). European Journal of Immunology, 24(12), 3140-7 (English) 1994. CODEN: EJIMAF. ISSN: 0014-2980. Publisher: VCH.

AB The authors investigated the ability of staphylococcal **enterotoxin** B (SEB) to modify the immediate hypersensitivity response induced in BALB/c mice following sensitization to ovalbumin (OVA), a response mediated by OVA-reactive Vβ8 T cells. Mice were sensitized by skin painting with OVA every second day over a period of 2 wk. SEB, a potent activator of Vβ8+ T cells, was administered at the same site where OVA was applied (skin of the lower abdomen) following two different protocols. In protocol (A) SEB was injected intradermally 1 day before painting with OVA and on day 7; in protocol B, SEB was injected each time OVA was applied to the skin (eight times). SEB (but not SEA) altered the development of immediate hypersensitivity to OVA, as demonstrated by the reduction in allergen-specific IgE, decreased OVA-specific immediate skin test responsiveness, and prevented the development of increased airway responsiveness after bronchial challenge with OVA. Injections of SEB did not alter the proliferative responses of local draining lymph node cells or spleen mononuclear cells to OVA, indicating that administration of SEB did not inhibit the sensitization to OVA, but shifted the immune response away from an immediate type response (IgE/IgG1) to IgG2a, IgG2b and IgG3. Although both protocols of SEB **treatment** did not lead to a major deletion of the Vβ8 T cell population, they did reduce the proliferative response of Vβ8+ T cells to OVA. These data indicate that the bacterial **toxin** SEB is capable of modifying the immediate hypersensitivity response induced by OVA by altering the functional capacity of antigen-reactive Vβ8 T cells.

L23 ANSWER 18 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN

1994:555532 Document No. 121:155532 The model of arthritis induced by superantigen in mice. Nagai, Hiroichi; Takaoka, Yuko; Kamada, Hiroyuki; Mori, Hiroshi (Dep. Pharmacology, Gifu Pharmaceutical Univ., Gifu, 502, Japan). Life Sciences, 55(12), PL233-PL237 (English) 1994. CODEN: LIFSAK. ISSN: 0024-3205.

AB S.c. injection of Staphylococcal **enterotoxin** B (SEB) produced by Staphylococcus aureus, caused severe arthritis in DBA/1J mice which had been previously immunized with bovine type II collagen. The severity of

this arthritis was dose dependent and prolonged joint inflammation with erosion of bone was observed Anti-type II collagen antibodies were detected in the serum of arthritic mice. Effector T cells against type II collagen were also detected by delayed type hypersensitivity in the skin. Moreover, a significant decrease in the ratio between T cells and B cells and an increase in the ratio between CD4+ cells and CD8+ cells was observed in spleen cells from arthritic mice. Prednisolone suppresses the induction and development of clin. signs of arthritis in mice. This evidence suggests that this exptl. arthritis model may provide a means to examine the role of superantigens and the efficacy of pharmacol. agents for the **treatment** of rheumatoid arthritis.

L23 ANSWER 19 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN
1991:115084 Document No. 114:115084 Antiallergy agents containing allergens and adjuvants and antiallergy agents containing allergen-adjuvant complexes. Watanabe, Naohiro (Japan). Jpn. Kokai Tokkyo Koho JP 02235823 A2 19900918 Heisei, 5 pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 1989-54887 19890309.

AB Antiallergy agents, which are useful for **treatment** of type I **allergy**, e.g. asthma and allergic rhinitis, and have low toxicity, contain (1) allergens and adjuvants stimulating production of IgA against the allergens; or (2) allergens bonded with the adjuvants (via spacers). Nasal administration of 10 μg ovalbumin and 1.0 μg cholera **toxin** produced antiovalbumin IgA in mice, vs. none, without the **toxin.**

L23 ANSWER 20 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN
1987:634622 Document No. 107:234622 Cysteinyl leukotrienes as mediators of staphylococcal **enterotoxin** B in the monkey. Scheuber, P. H.; Denzlinger, C.; Wilker, D.; Beck, G.; Keppler, D.; Hammer, D. K. (Biochem. Inst., Univ. Freiburg, Freiburg, Fed. Rep. Ger.). European Journal of Clinical Investigation, 17(5), 455-9 (English) 1987. CODEN: EJCIB8. ISSN: 0014-2972.

AB The role of cysteinyl leukotrienes (LTs) in the action of staphylococcal **enterotoxin** B (SEB) was investigated in unsensitized monkeys using inhibitors of prostanoid synthesis and LT action and by measuring generation of LT in vivo. LY 171883, a selective LTD4/LTE4 receptor antagonist, was highly efficient in inhibiting immediate-type hypersensitivity reactions in the skin and protecting against the emetic response provoked by SEB in a concentration-dependent manner. Inhibition of prostanoid formation by pretreatment of monkeys with indomethacin or aspirin did not influence SEB responses. Based on chromatog. and RIA, the generation of endogenous cysteinyl LTs was demonstrated in vivo. The concentration of LTE4, the major biliary cysteinyl LT detected, increased 10-fold and a novel cysteinyl LT metabolite in urine indicated strongly enhanced LT generation upon challenge with SEB. Cysteinyl LTs are important mediators in the pathophysiol. of SEB-induced enteric intoxication. Therefore, cysteinyl LT antagonists may be of therapeutic value in the **treatment** of this intestinal disorder.

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=> s enterotoxin
L24       46016 ENTEROTOXIN

=> s l24 and T helper 1 response
L25           0 L24 AND T HELPER 1 RESPONSE

=> s l24 and cytokine response
L26         293 L24 AND CYTOKINE RESPONSE

=> s l26 and allergy
L27           7 L26 AND ALLERGY

=> dup remove l27
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PROCESSING COMPLETED FOR L27
L28 5 DUP REMOVE L27 (2 DUPLICATES REMOVED)

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L28 ANSWER 1 OF 5 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
DUPLICATE 1
2004:367457 Document No.: PREV200400364324. High IFN-gamma production by CD8+ T cells and early sensitization among infants at high risk of atopy. Rowe, Julie; Heaton, Tricia; Kusel, Merci; Suriyaarachchi, Devinda; Serralha, Michael; Holt, Barbara J.; de Klerk, Nick; Sly, Peter D.; Holt, Patrick G. [Reprint Author]. Div Cell Biol, Telethon Inst Child Hlth Res, POB 855, W Perth, WA, 6872, Australia. patrick@ichr.uwa.edu.au. Journal of Allergy and Clinical Immunology, (April 2004) Vol. 113, No. 4, pp. 710-716. print. CODEN: JACIBY. ISSN: 0091-6749. Language: English.
AB Background: High genetic risk (HR) of atopy among unstratified populations of infants is associated with attenuated IFN-gamma responses. However, the role of IFN-gamma in progression from HR status to active disease is less clear. Objective: To identify immune function markers in neonates with HR that are associated with positive atopic outcomes at 2 years. Methods: Cord blood mononuclear cells (CBMCs) were collected from 175 children with HR and cryopreserved. The children were assessed for atopy by skin prick at 0.5 and 2 years. CBMCs were thawed and stimulated with allergens and mitogens PHA and staphylococcal **enterotoxin** B (SEB), and **cytokine responses** were determined.
Results: No correlations were observed between allergen specific CBMC responses and atopic outcomes. In contrast, sensitization was strongly associated with polyclonal IFN-gamma responses to both PHA (P=.002) and SEB (P =.005), and also with SEB-induced IL-5 (P=.05), IL-10 (P =.02), and IL-13 (P =.01). Logistic regression analysis identified elevated PHA-induced IFN-gamma and SEB-induced IL-13 responses as the strongest independent predictors of atopy development. Cell separation studies confirmed CD8+ T cells as the source of apprx90 % of IFN-gamma production. Conclusions: IFN-gamma produced by CD8+ T cells may synergize with TH2 cytokines in driving atopy development in children with HR.

L28 ANSWER 2 OF 5 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
2004:213024 Document No.: PREV200400214754. Effects of the macrolide antibiotic, midecamycin, on Staphylococcus aureus product-induced Th2 **cytokine response** in patients with atopic dermatitis.
Matsui, Katsuhiko [Reprint Author]; Nishikawa, Akemi [Reprint Author]. Department of Immunobiology, Meiji Pharmaceutical University, Kiyose, Tokyo, 204-8588, Japan. Journal of Interferon and Cytokine Research, (March 2004) Vol. 24, No. 3, pp. 197-201. print.
ISSN: 1079-9907 (ISSN print). Language: English.
AB In the present study, the effects of the macrolide antibiotic, midecamycin (MDM), on the Th2 **cytokine response** induced by the Staphylococcus aureus products, staphylococcal **enterotoxin** B (SEB), lipoteichoic acid (LTA), and peptidoglycan (PEG), was investigated in human peripheral blood mononuclear cells (PBMCs) from patients with atopic dermatitis (AD). MDM inhibited SEB-induced mRNA expression of the Th2 cytokines interleukin-4 (IL-4) and IL-5 in PBMCs from patients with AD. Furthermore, MDM also suppressed LTA-induced or PEG-induced IL-5 mRNA expression in these patients. Inhibition of mRNA expression by MDM correlated with the synthesis of cytokines in PBMCs, indicating that MDM controls Th2 cytokine production. In addition, S. aureus strains isolated from skin lesions of patients with AD were particularly susceptible to MDM compared with gentamicin, which is used widely in Japan as an antibiotic ointment combined with steroid for topical application in AD. These results suggest that topical administration of MDM might be beneficial in AD lesions infected with S. aureus.

L28 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
2003:656800 Document No. 139:191423 Immune-modulating peptide made of S. aureus **enterotoxin** B. Neuber, Karsten (Agelab Pharma G.m.b.H.,

Germany). PCT Int. Appl. WO 2003068812 A2 20030821, 46 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (German). CODEN: PIXXD2. APPLICATION: WO 2003-EP1511 20030214. PRIORITY: DE 2002-10207734 20020215; DE 2002-10240866 20020904.

AB The invention relates particularly to peptides which are specifically capable of binding IgE antibodies and can be obtained from naturally occurring S. aureus **enterotoxin** B (SEB), for example. The immune-modulating properties thereof are substantially different from those of bacterial SEB. Surprisingly, the inventive peptides do not induce proliferation of T cells, as opposed to SEB. Due to their properties, said peptides are suitable for treating diseases that are characterized by an increased serum IgE level and/or an increased production of interferon gamma and for treating diseases that are characterized by an imbalance in the Th1 and Th2 **cytokine response**, e.g. atopic eczema, lupus erythematosus, Crohn's disease, multiple sclerosis, psoriasis, and rheumatoid arthritis.

L28 ANSWER 4 OF 5 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

2003:227612 Document No.: PREV200300227612. Specific patterns of responsiveness to microbial antigens staphylococcal **enterotoxin** B and purified protein derivative by cord blood mononuclear cells are predictive of risk for development of atopic dermatitis. Sharp, M. J.; Rowe, J.; Kusel, M.; Sly, P. D.; Holt, P. G. [Reprint Author]. Division of Cell Biology, TVW Telethon Institute for Child Health Research, PO Box 855, West Perth, WA, 6872, Australia. patrick@ichr.uwa.edu.au. Clinical and Experimental Allergy, (April 2003) Vol. 33, No. 4, pp. 435-441. print. ISSN: 0954-7894 (ISSN print). Language: English.

AB Background: Mononuclear cells from children with active atopic dermatitis (AD) have been reported to be hyper-responsive to certain microbial stimuli, in particular staphylococcal **enterotoxin** B (SEB). However, it is not known whether this responsiveness is acquired during disease development, or is inherent. We investigated this question in a cohort of children at high risk of atopy followed prospectively from birth to age 3 years. We asked whether their cord blood mononuclear cell (CBMC) **cytokine responses** to SEB, to an unrelated microbial stimulus purified protein derivative (PPD), or to common allergens, were predictive of risk for subsequent AD development during infancy. Methods: Children at high risk of developing atopy were randomly selected from an ongoing prospective cohort. Cord blood was collected at birth. The children were seen at 6 months, 1, 2 and 3 years and examined for the development of AD. IFN-gamma, IL-5, IL-10 and IL-13 production by CBMC cultured in the presence of SEB, PPD, PHA, house dust mite (HDM) allergen, ovalbumin (OVA) and cat allergen was determined. Results: SEB-induced IL-5 production by CBMC was elevated in children who developed AD at 6 months (P=0.01) and 2 years (P=0.009). PPD-induced IL-5 responses were also elevated in CBMC from children who developed AD at 6 months, 2 years and 3 years (P=0.05, P=0.06 and P=0.06, respectively), as were PPD-induced IL-10 responses (P=0.05 at 1 years, P=0.007 at 2 years, P=0.003 at 3 years) and corresponding IFN-gamma responses (P=0.05 at 6 months, P=0.003 at 2 years, P=0.0004 at 3 years). Increased IL-10 responses to HDM allergen were also observed throughout the observation period in CBMC from children who developed AD. Conclusion: Children who develop infantile AD appear to have a predisposition to respond to SEB in a Th2-dominant manner involving selective stimulation of IL-5 production. The increased IL-10 and IFN-gamma induced in response to PPD by children with AD may point to additional intrinsic differences in responses to microbial stimuli between those at high vs. those at low risk for AD, which merit more detailed investigations.

L28 ANSWER 5 OF 5 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
DUPLICATE 2
2002:623128 Document No.: PREV200200623128. Polyclonal and allergen-induced **cytokine responses** in children with elevated immunoglobulin E but no atopic disease. Smart, J. M.; Tang, M. L. K.; Kemp, A. S. [Reprint author]. Department of Immunology, Royal Children's Hospital, Flemington Road, Parkville, VIC, 3052, Australia. kempa@cryptic.rch.unimelb.edu.au. Clinical and Experimental Allergy, (November, 2002) Vol. 32, No. 11, pp. 1552-1557. print. ISSN: 0954-7894. Language: English.

AB Background: Reduced Th1 and elevated Th2 **cytokine responses** are considered to be a principal mechanism in the generation of the inflammation leading to the manifestations of atopic disease in the skin of atopic dermatitis and in the airways of asthma. If reduced Th1 and elevated Th2 responses are principal determinants of the manifestation of atopic disease it might be expected that subjects with established disease would exhibit differences in their cytokine profiles as compared with atopic patients without clinical disease. Objective: To determine whether asymptomatic atopic children exhibit a cytokine imbalance similar to that seen in patients with established atopic disease or if they behave like non-atopic controls. **Cytokine responses** in a group of children with elevated IgE but no clinical manifestations of disease, atopic children with established disease and non-atopic controls were compared. Methods: We examined allergen-induced (house dust mite, HDM, rye grass pollen and RYE) **cytokine responses** in parallel with polyclonal (staphylococcal **enterotoxin** B, SEB) **cytokine responses** in a group of children with elevated serum IgE levels without current or past evidence of atopic disease (median age 6.6 years) and compared these with a non-atopic control group (median age 6.5 years) and a group of children with atopic disease (median age 6.7 years). Results: Symptomatic atopic children had reduced SEB-induced IFN-gamma and increased SEB-induced IL-4 and IL-5 as compared with non-atopic controls. In contrast, SEB-induced IFN-gamma, IL-4 and IL-5 production in asymptomatic atopics was not significantly different from the non-atopic control subjects. Allergen-induced Th1 (IFN-gamma) and Th2 (IL-5 and IL-13) cytokine production was increased in both symptomatic atopics and asymptomatic atopics when compared with non-atopic controls. Conclusion: The defect in polyclonally induced IFN-gamma production was associated with the clinical manifestation of atopic disease but not the atopic state per se. This suggests that the global reduction in IFN-gamma is the key determinant of the development of overt atopic disease. In contrast, elevated allergen-induced Th2 **cytokine responses** in children related to the atopic state per se irrespective of the presence of clinical atopic disease.

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L29         11 CHLOERA TOXIN

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L30      46965 CHOLERA TOXIN

=> s l30 and cytokine response
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L34 ANSWER 1 OF 1 MEDLINE on STN DUPLICATE 1
2004440854. PubMed ID: 15347376. Mixed antibody and T cell responses to peanut and the peanut allergens Ara h 1, Ara h 2, Ara h 3 and Ara h 6 in an oral sensitization model. van Wijk F; Hartgring S; Koppelman S J; Pieters R; Knippels L M J. (Institute for Risk Assessment Sciences, Immunotoxicology, Utrecht University, Utrecht, The Netherlands.) Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology, (2004 Sep) 34 (9) 1422-8. Journal code: 8906443. ISSN: 0954-7894. Pub. country: England: United Kingdom. Language: English.
AB BACKGROUND: Peanut **allergy** is known for its severity and persistence through life. Several peanut proteins have been identified as allergenic and are indicated as Ara h 1-7. Very little is known about the mechanisms that underlie sensitization to peanut proteins. OBJECTIVE: The purpose of the present study was to reveal the immune responses that are induced against peanut and the peanut allergens Ara h 1, Ara h 2, Ara h 3 and Ara h 6 during sensitization, including the very early responses. METHODS: Humoral and T cell responses against peanut and the peanut allergens were examined in an early and later stage of sensitization in an established murine model of peanut anaphylaxis. Therefore C3H/HeJ mice were orally exposed to two different doses of peanut extract plus **cholera toxin.** RESULTS: Oral sensitization to peanut was characterized by an antigen-induced mixed **cytokine response** in the spleen (IL-4, IL-5, IL-10 and IFN-gamma), which could already be observed 7 days after the onset of exposure. Additionally, polyisotypic humoral responses (IgE, IgG1 and IgG2a) against peanut were found in the serum. Moreover, we demonstrated that these **T helper** (Th)1/Th2 cytokine and antibody responses were also directed specifically against the major peanut allergens Ara h 1, Ara h 2, Ara h 3 and Ara h 6. CONCLUSIONS: This study implicates that both Th1 and Th2 phenomena are involved in the development of peanut **allergy** in the C3H/HeJ murine model. Furthermore, we show that the present oral model is suitable to examine immune responses to food allergens during different stages of sensitization upon treatment with a whole food extract.

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L35 ANSWER 1 OF 11 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
2004:1078931 The Genuine Article (R) Number: 875GS. Protection against influenza virus infection by intranasal administration of hemagglutinin vaccine with chitin microparticles as an adjuvant. Hasegawa H (Reprint); Ichinohe T; Strong P; Watanabe I; Ito S; Tamura S; Takahashi H; Sawa H; Chiba J; Kurata T; Sata T. Natl Inst Infect Dis, Dept Pathol, 4-7-1 Gakuen, Tokyo 2080011, Japan (Reprint); Natl Inst Infect Dis, Dept Pathol, Tokyo 2080011, Japan; Sci Univ Tokyo, Dept Biol Sci & Technol, Noda, Chiba 278, Japan; Univ Oxford, MRC, Immunochem Unit, Oxford, England; Osaka Univ, Res Inst Microbial Dis, Lab Prevent Viral Dis, Osaka, Japan; Hokkaido Univ, Cent COE Program Zoonosis Control 21, Lab Mol & Cellular Pathol, Sapporo, Hokkaido, Japan; CREST, JST, Sapporo, Hokkaido, Japan. hasegawa@nih.go.jp. JOURNAL OF MEDICAL VIROLOGY (JAN 2005) Vol. 75, No. 1, pp. 130-136. ISSN: 0146-6615. Publisher: WILEY-LISS, DIV JOHN WILEY & SONS INC, 111 RIVER ST, HOBOKEN, NJ 07030 USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Chitin in the form of microparticles (chitin microparticles, CMP) has been demonstrated to be a potent stimulator of macrophages, promoting **T-helper**-1 (Th1) activation and **cytokine**

response. In order to examine the mucosal adjuvant effect of CMP co-administered with influenza hemagglutinin (HA) vaccine against influenza infection, CMP were intranasally co-administered with influenza HA vaccine prepared from PR8 (H1N1) virus. Inoculation of the vaccine with CMP induced primary and secondary anti-HA IgA responses in the nasal wash and anti-HA IgG responses in the serum, which were significantly higher than those of nasal vaccination without CMP, and provided a complete protection against a homologous influenza virus challenge in the nasal infection influenza model. In addition, CMP-based immunization using A/Yamagata (H1N1) and A/Guizhou (H3N2) induced PR8 HA-reactive IgA in the nasal washes and specific-IgG in the serum. The immunization with A/Yamagata and CMP resulted in complete protection against a PR8 (H1N1) challenge in A/Yamagata (H1N1)-vaccinated mice, while that with A/Guizhou (H3H2) and CMP exhibited a 100-fold reduction of nasal virus titer, demonstrating the cross-protective effect of CMP and influenza vaccine. It is suggested that CMP provide a safe and effective adjuvant for nasal vaccination with inactivated influenza vaccine. (C) 2005 Wiley-Liss, Inc.

L35 ANSWER 2 OF 11 MEDLINE on STN DUPLICATE 1

2004440854. PubMed ID: 15347376. Mixed antibody and T cell responses to peanut and the peanut allergens Ara h 1, Ara h 2, Ara h 3 and Ara h 6 in an oral sensitization model. van Wijk F; Hartgring S; Koppelman S J; Pieters R; Knippels L M J. (Institute for Risk Assessment Sciences, Immunotoxicology, Utrecht University, Utrecht, The Netherlands.) Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology, (2004 Sep) 34 (9) 1422-8. Journal code: 8906443. ISSN: 0954-7894. Pub. country: England: United Kingdom. Language: English.

AB BACKGROUND: Peanut allergy is known for its severity and persistence through life. Several peanut proteins have been identified as allergenic and are indicated as Ara h 1-7. Very little is known about the mechanisms that underlie sensitization to peanut proteins. OBJECTIVE: The purpose of the present study was to reveal the immune responses that are induced against peanut and the peanut allergens Ara h 1, Ara h 2, Ara h 3 and Ara h 6 during sensitization, including the very early responses. METHODS: Humoral and T cell responses against peanut and the peanut allergens were examined in an early and later stage of sensitization in an established murine model of peanut anaphylaxis. Therefore C3H/HeJ mice were orally exposed to two different doses of peanut extract plus **cholera toxin.** RESULTS: Oral sensitization to peanut was characterized by an antigen-induced mixed **cytokine response** in the spleen (IL-4, IL-5, IL-10 and IFN-gamma), which could already be observed 7 days after the onset of exposure. Additionally, polyisotypic humoral responses (IgE, IgG1 and IgG2a) against peanut were found in the serum. Moreover, we demonstrated that these **T helper** (Th)1/Th2 cytokine and antibody responses were also directed specifically against the major peanut allergens Ara h 1, Ara h 2, Ara h 3 and Ara h 6. CONCLUSIONS: This study implicates that both Th1 and Th2 phenomena are involved in the development of peanut allergy in the C3H/HeJ murine model. Furthermore, we show that the present oral model is suitable to examine immune responses to food allergens during different stages of sensitization upon treatment with a whole food extract.

L35 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2005 ACS on STN

2005:108073 Document No. 142:314848 Transcutaneous immunization with P. gingivalis surface protein antigen induces I helper 2 responses in systemic tissues. Maeba, Satomi; Otake, Shigeo; Namikoshi, Jun; Hayakawa, Mitsuo; Abiko, Yoshimitsu; Yamamoto, Masafumi (Clinical Pathology, Nihon University Graduate School of Dentistry at Matsudo, Chiba, 271 8587, Japan). International Journal of Oral-Medical Sciences, 3(2), 67-74 (English) 2004. CODEN: IJOSC7. ISSN: 1347-9733. Publisher: Research Institute of Oral Science, Nihon University School of Dentistry at Matsudo.

AB Porphyromonus gingivalis is a major pathogen of chronic periodontitis. An outer membrane protein with a mol. mass of 40-kDa (40k-OMP) is a highly immunogenic surface protein produced by P. gingivalis. In this study, to

develop an effective vaccine against P. gingivalis infection, we assessed **T helper** (Th) cell responses in systemic and mucosal compartments after 40k-OMP was administered transcutaneously. When CD4+ T cells isolated from the spleens of mice immunized with 40k-OMP alone or 40k-OMP plus **cholera toxin** were restimulated with 40k-OMP in vitro, significant levels of proliferative responses were induced. In contrast, only low levels of CD4+ T cell proliferation were induced in cervical lymph nodes. Anal. of Th1 [interferon (IFN)-γ] and Th2 [interleukin (IL)-4, IL-5, and IL-6] **cytokine responses** showed that 40k-OMP-specific Th cells from the spleen produced significant levels of IL-4, IL-5, and IL-6 but did not trigger changes in IFN-γ production These results suggest that transcutaneous administration of 40k-OMP can elicit 40k-OMP-specific Th2-type **cytokine responses** in systemic, but not mucosal, lymphoid tissues.

L35 ANSWER 4 OF 11 MEDLINE on STN DUPLICATE 2

2003339014. PubMed ID: 12871182. Therapeutic manipulation of the immune system: enhancement of innate and adaptive mucosal immunity. Boyaka Prosper N; Tafaro Angela; Fischer Romy; Fujihashi Kohtaro; Jirillo Emilio; McGhee Jerry R. (Department of Microbiology, and The Immunobiology Vaccine Center, The University of Alabama at Birmingham, Birmingham, Alabama 35294-2170, USA.. prosper@uab.edu) . Current pharmaceutical design, (2003) 9 (24) 1965-72. Ref: 118. Journal code: 9602487. ISSN: 1381-6128. Pub. country: Netherlands. Language: English.

AB The mucosal immune system has evolved alongside, but separate, from the general systemic immune system. As a major consequence of this dichotomy, only immune responses initiated in mucosal inductive sites can result in effective immunity in mucosal tissues themselves. Oral tolerance, as usually assessed as orally-induced systemic unresponsiveness, contributes to mucosal homoeostasis by preventing unwanted immune reactions to food or environmental antigens. It is now established that tolerance can also be induced by the nasal route and mucosally-induced tolerance is being actively investigated for immune therapy against a number of diseases. Nontoxic derivatives of **cholera toxin** and the heat labile toxin of Escherichia coli as well as chimeric enterotoxins have been developed. These molecules retain the mucosal adjuvant activity of native enterotoxins and are effective at inducing targeted Th1 or Th2-type immune responses. Mucosal delivery of cytokines as adjuvants represents a safer alternative to parenteral cytokine injection. Nasally administered cytokines such as IL-1 and IL-12 or chemokines including RANTES, lymphotactin, MIP-1 beta, all act as mucosal adjuvants for co-administered antigens. Each of these cytokines promote specific pattern of CD4(+) **T helper** cell **cytokine responses** that could be exploited for targeted immune therapy. Although GALT and NALT are both parts of the Common Mucosal Immune System, there are major differences between orally and nasally induced immune responses. Nasal vaccines more effectively promote protective immunity in the genitourinary tract than do oral vaccines. In addition, aging affects mucosal tolerance or immunity in GALT more than is seen in NALT. Therapeutic manipulation of mucosal immunity involves regulation of CD4(+) T cell **cytokine responses** and thus, should require a careful examination of the host status, including the occurrence of inflammatory bowel diseases.

L35 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2005 ACS on STN

2004:98303 Document No. 140:251996 Nasal immunization with P. gingivalis surface protein antigen and **cholera toxin** adjuvant induces **T helper** 2 responses in both mucosal and systemic compartments. Namikoshi, Jun; Maeba, Satomi; Yamamoto, Masafumi; Hayakawa, Mitsuo; Abiko, Yoshimitsu; Otake, Shigeo (Clinical Pathology, Nihon University Graduate School of Dentistry at Matsudo, Chiba, 271-8587, Japan). International Journal of Oral-Medical Sciences, 1(2), 90-96 (English) 2003. CODEN: IJOSC7. ISSN: 1347-9733. Publisher: Research Institute of Oral Science, Nihon University School of Dentistry at

Matsudo.

AB It is well established that Porphyromonas gingivalis is one of the major pathogens of adult periodontitis. P. gingivalis produces an outer membrane protein with a mol. mass of 40-kDa (40k-OMP). Here, to assess the potential for application of 40k-OMP in the development of an anti-periodontal disease vaccine, the authors analyzed 40k-OMP-specific CD4+ **T helper** (Th) cell responses induced in the mucosal as well as systemic compartments when 40k-OMP was administered nasally. When CD4+ T cells that were isolated from cervical lymph nodes (CLN) and spleens of mice immunized with 40k-OMP plus **cholera toxin** (CT) as adjuvant were re-stimulated with 40k-OMP in vitro, significant levels of proliferative responses were induced. In contrast, essentially no increased proliferation occurred in CLN and spleens taken from mice given 40k-OMP alone. Anal. of **T helper** (Th) 1 (IFN-γ) and Th2 (IL-4, IL-5, and IL-6) **cytokine responses** showed that 40k-OMP-specific Th cells from both CLN and the spleen produced significant levels of IL-4, IL-5, and IL-6 but did not result in changes in IFN-γ production In contrast, marginal levels of IL-4, IL-5, and IL-6 production were seen in mice given 40k-OMP alone nasally. Thus, nasal administration of 40k-OMP plus CT as an adjuvant can elicit 40k-OMP-specific Th2-type **cytokine responses** in both mucosal and systemic compartments. Further, the nasal 40k-OMP vaccine has the potential as antiperiodontal vaccine.

L35 ANSWER 6 OF 11 MEDLINE on STN DUPLICATE 3

2002186497. PubMed ID: 11918690. Immunoglobulin A-deficient mice exhibit altered **T helper** 1-type immune responses but retain mucosal immunity to influenza virus. Zhang Yongxin; Pacheco Susan; Acuna Catherine L; Switzer Kirsten C; Wang Ying; Gilmore Xyanthine; Harriman Gregory R; Mbawuike Innocent N. (Influenza Research Center, Respiratory Pathogens Research Unit, Department of Molecular Virology, Baylor College of Medicine, Houston, Texas 77030, USA.) Immunology, (2002 Mar) 105 (3) 286-94. Journal code: 0374672. ISSN: 0019-2805. Pub. country: England: United Kingdom. Language: English.

AB We have previously demonstrated that immunoglobulin A (IgA)(-/-) knockout (KO) mice exhibit levels of susceptibility to influenza virus infection that are similar to those of their normal IgA(+/+) littermates. To understand the mechanism of this apparent mucosal immunity without IgA, immunoglobulin isotype and **T helper** 1 (Th1)-type [interferon-gamma (IFN-gamma)] and Th2-type [interleukin (IL)-4, IL-5)] **cytokine responses** to influenza vaccine were evaluated. Intranasal immunization with influenza virus subunit vaccine plus **cholera toxin/cholera toxin** B subunit (CT/CTB) induced significant influenza virus-specific immunoglobulin G (IgG) antibody in the serum and nasal passages of both IgA(-/-) and IgA(+/+) mice, while IgA antibodies were induced only in IgA(+/+) mice. IgA KO mice exhibited an IgG1 subclass haemagglutinin (HA)-specific response but no detectable IgG2a and IgG2b responses. In contrast, IgA(+/+) mice exhibited significant IgG1 as well as IgG2a responses. This indicates a predominant Th2-type response in IgA KO mice compared to normal mice. Following stimulation with influenza virus in vitro, splenic lymphocytes from immunized IgA(-/-) mice produced significantly lower levels of IFN-gamma than IgA(+/+) mice ($P < 0.001$), but elaborated similar levels of IL-4 and IL-5. This was true at both protein and mRNA levels. Immunized mice were challenged intranasally with a small inoculum of influenza virus to allow deposition of virus in the nasal mucosal passages. Compared to non-immunized mice, immunized IgA(-/-) and IgA(+/+) mice exhibited significant, but similar levels of reduction in virus titres in the nose and lung. These results demonstrate that in addition to IgA deficiency, IgA gene deletion also resulted in down-regulated Th1-type immune responses and confirm our previous data that IgA antibody is not indispensable for the prevention of influenza virus infection.

L35 ANSWER 7 OF 11 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on

STN
1998:765904 The Genuine Article (R) Number: 125NN. **T-helper** 1 and **T-helper** 2 **cytokine responses** in gut-associated lymphoid tissue following enteric reovirus infection. Fan J Y; Boyce C S; Cuff C F (Reprint). W Virginia Univ, Dept Microbiol & Immunol, Robert C Byrd Hlth Sci Ctr, Box 9177, Morgantown, WV 26506 USA (Reprint); W Virginia Univ, Dept Microbiol & Immunol, Robert C Byrd Hlth Sci Ctr, Morgantown, WV 26506 USA. CELLULAR IMMUNOLOGY (25 AUG 1998) Vol. 188, No. 1, pp. 55-63. ISSN: 0008-8749. Publisher: ACADEMIC PRESS INC, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495 USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Enteric infection of mice with reovirus serotype 1 elicits antibody and cytotoxic T-lymphocytes in gut-associated lymphoid tissue (GALT). This led to the hypothesis that **T-helper** 1 (Th1) and **T-helper** 2 (Th2) responses develop in GALT. Reverse transcriptase-polymerase chain reactions on RNA from Peyer's patches (PP), intraepithelial lymphocytes (IEL), and lamina propria (LP) lymphocytes demonstrated that interferon (IFN)-gamma message was increased in PP and IEL, but not in LP following infection. No increase in mRNA for interleukin (IL)-4, IL-5, or IL-6 was detected. IFN-gamma, IL-5, and IL-6 were produced in in vitro cultures of PP 4-10 days postinfection. PP and spleen lymphocytes from infected mice produced IFN-gamma, but no IL-5 following in vitro restimulation. Infection also induced production of mRNA for the beta 2 chain of the IL-12 receptor in PP. We conclude that reovirus induces robust Th1 and weak Th2 cell responses in GALT. a 1998 Academic Press.

L35 ANSWER 8 OF 11 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
1997:274789 Document No.: PREV199799566507. Intranasal administration of Schistosoma mansoni adult worm antigen in combination with **cholera toxin** induces a Th2 cell response. Akhiani, A. A.; Nilsson, L. A. [Reprint author]; Ouchterlony, O.. Dep. Med. Microbiol. Immunol., Univ. Goteborg, S413 46 Goteborg, Sweden. Parasite Immunology (Oxford), (1997) Vol. 19, No. 4, pp. 183-190.
CODEN: PAIMD8. ISSN: 0141-9838. Language: English.

AB Mice immunized with soluble adult worm antigen (SWAP) in combination with **cholera toxin** (CT) displayed significantly larger numbers of IgG1, IgM and IgA secreting cells in the spleen and in the lungs as compared to mice which had received SWAP only. The ratio of SWAP-specific IgG1 to IgG2a antibody-secreting spleen cells was also significantly higher in the SWAP-CT group. Analysis of **cytokine responses** revealed that SWAP-stimulated spleen and lung cells from the SWAP-CT group produced lower levels of IFN-gamma but higher levels of IL-4 and IL-5 as compared to cells from the SWAP group. These findings indicate that intranasal administration of SWAP-CT induces a Th2 cell response in the spleen and in the lungs. Our findings also suggest that CT was responsible for induction of this Th2 cell response, since intranasal administration of SWAP alone induced a Th1 type response in the spleen and in the lungs.

L35 ANSWER 9 OF 11 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
1996:110396 The Genuine Article (R) Number: TU692. Regulation of mucosal and systemic antibody responses by **T helper** cell subsets, macrophages, and derived cytokines following oral immunization with live recombinant Salmonella. VanCott J L (Reprint); Staats H F; Pascual D W; Roberts M; Chatfield S N; Yamamoto M; Coste M; Carter P B; Kiyono H; McGhee J R. UNIV ALABAMA, MED CTR, DEPT MICROBIOL, BIRMINGHAM, AL 35294; UNIV ALABAMA, MED CTR, DEPT ORAL BIOL, BIRMINGHAM, AL 35294; UNIV ALABAMA, MED CTR, IMMUNOBIOL VACCINE CTR, BIRMINGHAM, AL 35294; DUKE UNIV, MED CTR, DEPT MED, DURHAM, NC 27710; UNIV LONDON IMPERIAL COLL SCI TECHNOL & MED, DEPT BIOCHEM, LONDON SW7 2AY, ENGLAND; MEDEVA, VACCINE RES UNIT, LONDON SW7 2AY, ENGLAND; INRA, JOUY EN JOSAS, FRANCE; OSAKA UNIV, MICROBIAL DIS RES INST, DEPT MUCOSAL IMMUNOL, SUITA, OSAKA 565, JAPAN. JOURNAL OF IMMUNOLOGY (15 FEB 1996) Vol. 156, No. 4, pp. 1504-1514. ISSN: 0022-1767.

Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We have assessed regulatory Th cell and **cytokine responses** in mice after oral immunization with recombinant Salmonella (BRD 847) expressing fragment C of tetanus toroid, since little information is available to explain how these vectors induce mucosal IgA responses. A single dose of BRD 847 elicited serum IgG2a and mucosal IgA anti-tetanus toroid Ab responses. To assess Th1- and Th2-type responses, CD4(+) T cells from Peyer's patches and spleen were restimulated in vitro, and cytokine-specific ELISPOT, ELISA, and reverse transcriptase-PCR assays were used to assess cytokine patterns. CD4(+) T cells produced IFN-gamma and IL-2 as well as IL-10, but not IL-4 or IL-5. Although IL-6 was elevated, further purification of cells from in vitro cultures into CD4(+) Mac-1(-) T cells and Mac-1(+) CD4(-) cells revealed that only the latter cell population had consistently elevated IL-6 gene expression, whereas both sorted populations exhibited increased IFN-gamma and IL-10 gene expression. Thus, orally administered recombinant Salmonella expressing fragment C of tetanus toroid elicited dominant Ag-specific Th1-type responses together with Th2-type cells producing IL-10 in both mucosal and systemic tissues. Macrophages producing IL-6 were also evident. Our results are consistent with the suggestion that Ag-specific Th1 cells and their derived cytokines, IFN-gamma and IL-2, and Th2-derived IL-10 together with IL-6 produced by macrophages provide important signals for the development of mucosal IgA and serum Ige subclass responses in the absence of preferential expression of Th2 cytokines IL-4 and IL-5.

L35 ANSWER 10 OF 11 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

1996:248427 The Genuine Article (R) Number: UC314. Epitope maps of the Escherichia coli heat-labile toxin B subunit for development of a synthetic oral vaccine. Takahashi I (Reprint); Kiyono H; Jackson R J; Fujihashi K; Staats H F; Hamada S; Clements J D; Bost K L; McGhee J R. OSAKA UNIV, FAC DENT, DEPT ORAL MICROBIOL, 1-8 YAMADAOKA, SUITA, OSAKA 565, JAPAN (Reprint); UNIV ALABAMA, MED CTR, DEPT MICROBIOL, IMMUNOBIOL VACCINE CTR, MUCOSAL IMMUNIZAT RES GRP, BIRMINGHAM, AL 35294; UNIV ALABAMA, MED CTR, DEPT ORAL BIOL, BIRMINGHAM, AL 35294; DUKE UNIV, MED CTR, DURHAM, NC 27710; TULANE UNIV, SCH MED, DEPT MICROBIOL & IMMUNOL, NEW ORLEANS, LA 70112. INFECTION AND IMMUNITY (APR 1996) Vol. 64, No. 4, pp. 1290-1298. ISSN: 0019-9567. Publisher: AMER SOC MICROBIOLOGY, 1325 MASSACHUSETTS AVENUE, NW, WASHINGTON, DC 20005-4171. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Linear B- and T-cell epitopes spanning all 103 amino acids of the Escherichia coli heat-labile toxin B subunit (LT-B) were assessed in mice orally immunized with native LT or with recombinant Salmonella enteritidis expressing LT-B. Oral administration of native LT induced mucosal immunoglobulin A (IgA) antibodies reactive with an epitope at residues 85 to 91, while IgA induced by recombinant Salmonella LT-B reacted with an epitope at residues 36 to 44. Serum Ige anti-LT-B antibodies from mice orally immunized with either LT or with recombinant Salmonella LT-B were directed to both epitopes. A single T-cell epitope spanning residues 34 to 42 was identified by T-cell proliferative and **cytokine responses**. When a 20-mer peptide (residues 26 to 45) with B- and T-cell epitopes was given orally to BALB/c (H-2(d)) and B10 congenic (I-A(d), I-A(b), and I-A(k)) mice, significant fecal IgA and serum IgG anti-LT-B antibodies were induced. The peptide also induced LT-B-specific T-cell proliferative responses in these mice. Orally administered LT-B peptide (residues 26 to 45) induced a cytokine profile indicative of both **T helper** 1- and 2-type cells. The remarkable immunogenicity of this 20-mer peptide makes it a candidate for a vaccine to protect against enterotoxigenic E. coli.

L35 ANSWER 11 OF 11 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

1996:837618 The Genuine Article (R) Number: VT756. Saponin adjuvant primes

for a dominant interleukin-10 production to ovalbumin and to Trypanosoma cruzi antigen. Tadokoro C E (Reprint); Macedo M S; Abrahamsohn I A. UNIV SAO PAULO, INST CIENCIAS BIOMED, DEPT IMMUNOL, BR-05508900 SAO PAULO, BRAZIL. IMMUNOLOGY (NOV 1996) Vol. 89, No. 3, pp. 368-374. ISSN: 0019-2805 . Publisher: BLACKWELL SCIENCE LTD, OSNEY MEAD, OXFORD, OXON, ENGLAND OX2 0EL. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The adjuvant activity of saponin for T-cell responses was evaluated and compared with that of complete Freund's adjuvant (CFA) in two antigen systems: a lysate of the protozoa Trypanosoma cruzi and ovalbumin (OA). Strong delayed-type hypersensitivity and T-cell proliferate responses, comparable with those stimulated by CFA, were observed for both antigens following immunization with saponin as adjuvant, Upon in vitro secondary antigen stimulation, high interleukin-10 (IL-10) and low interferon-gamma (IFN-gamma) levels were observed in lymph node (LN) cell cultures from saponin-immunized mice in contrast with the high IFN-gamma and decreased IL-10 production by LN cells from CFA-immunized mice. Production of IL-10 and IFN-gamma in these conditions was CD4-activation dependent, Concanavalin A (Con A)-stimulated interleukin-4 (IL-4) production was higher in saponin-immunized mice than in CFA-immunized mice. IL-10 produced by LN cells from saponin-immunized mice suppressed IFN-gamma production and Con A-induced proliferation, Taken together, these data are consistent with in vivo stimulation of both **T-helper** (Th)1 and Th2-type cells by immunization with saponin, in vitro a Th2-type **cytokine response** with high IL-10 production predominates, indicating preferential priming towards a Th2-type response, Immunization with CFA induced a Th1-type **cytokine response.** To our knowledge, this is the first report in which an adjuvant is shown to prime for a dominant IL-10 production.

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FULL ESTIMATED COST	339.41	339.62

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